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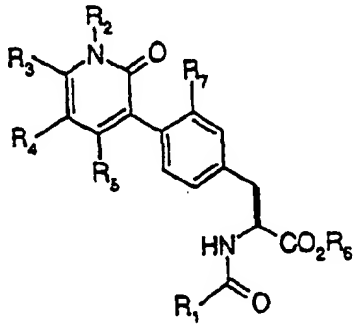
(54) Title: 4-PYRIDINYL-N-ACYL-L-PHENYLALANINES



(I)

(57) Abstract: Compounds of Formula (I) are disclosed wherein R_1-R_7 are as defined in the application and which have activity as inhibitors of binding between VCAM-1 and cells expressing VLA-4 and, therefore, are useful for treating diseases whose symptoms and or damage are related to the binding of VCAM-1 to cells expressing VLA-4, such as chronic inflammatory diseases.

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4-PYRIDINYL-N-ACYL-L-PHENYLALANINES

Vascular cell adhesion molecule-1 (VCAM-1), a member of the immunoglobulin (Ig) supergene family, is expressed on activated, but not resting, endothelium. The integrin VLA-4 ($\alpha_4\beta_1$), which is expressed on many cell types including circulating lymphocytes, eosinophils, basophils, and monocytes, but not neutrophils, is the principal receptor for VCAM-1. Antibodies to VCAM-1 or VLA-4 can block the adhesion of these mononuclear leukocytes, as well as melanoma cells, to activated endothelium *in vitro*. Antibodies to either protein have been effective at inhibiting leukocyte infiltration and preventing tissue damage in several animal models of inflammation. Anti-VLA-4 monoclonal antibodies have been shown to block T-cell emigration in adjuvant-induced arthritis, prevent eosinophil accumulation and bronchoconstriction in models of asthma, and reduce paralysis and inhibit monocyte and lymphocyte infiltration in experimental autoimmune encephalitis (EAE). Anti-VCAM-1 monoclonal antibodies have been shown to prolong the survival time of cardiac allografts. Recent studies have demonstrated that anti-VLA-4 mAbs can prevent insulitis and diabetes in non-obese diabetic mice, and significantly attenuate inflammation in the cotton-top tamarin model of colitis. It has further been shown that VCAM is expressed on endothelial cells of inflamed colonic tissue in a TNB/ethanol rat model of inflammatory bowel disease (*Gastroenterology* 1999, *116*, 874–883).

Thus, compounds which inhibit the interaction between α_4-containing integrins and VCAM-1 will be useful as therapeutic agents for the treatment of chronic inflammatory diseases such as rheumatoid arthritis (RA), multiple sclerosis (MS), asthma, and inflammatory bowel disease (IBD). The compounds of the present invention do have this effect.

As used in this specification, the term "halogen" means any of the four halogens, bromine, chlorine, fluorine, and iodine unless indicated otherwise. Preferred halogens are bromine, fluorine, and chlorine.

The term "lower alkyl", alone or in combination, means a straight-chain or branched-chain alkyl group containing one up to a maximum of six carbon atoms (C1-C6), such as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec.butyl, isobutyl, tert.butyl, n-pentyl, n-hexyl and the like.

The term a "substituted lower alkyl" means a lower alkyl group as defined before which is substituted by one or more groups selected independently from cycloalkyl, nitro, aryloxy, aryl, hydroxy, halogen, cyano, lower alkoxy, lower alkanoyl, lower alkylthio, lower alkyl sulfinyl, lower alkyl sulfonyl, amino or mono- or di-lower alkyl amino. Examples of substituted lower alkyl groups include 2-hydroxylethyl, 3-oxobutyl, cyanomethyl, and 2-nitropropyl. Although this invention is specifically directed to the substituted lower alkyl group trifluoromethyl at positions R_3 and R_5, pentafluoroethyl is also contemplated at these positions. This is also true of R_{22} and R_{23}.

The term "cycloalkyl" (or lower cycloalkyl) means an unsubstituted or substituted 3- to 7-membered carbacyclic ring. Substituents useful in accordance with the present invention are hydroxy, halogen, cyano, lower alkoxy, lower alkanoyl, lower alkyl, aroyl, lower alkylthio, lower alkyl sulfinyl, lower alkyl sulfonyl, aryl, heteroaryl and mono- or di lower alkyl substituted amino.

The term "lower alkenyl" means an alkylene group having from 2 to 10 carbon atoms with a double bond located between any two adjacent carbon atoms.

The term "lower alkoxy" means a straight-chain or branched-chain alkoxy group containing a maximum of six carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy and the like.

The term "lower alkylthio" means a lower alkyl group bonded to the rest of the molecule through a divalent sulfur atom, for example, a methyl mercapto or a isopropyl mercapto group. The term "lower alkylsulfinyl" means a lower alkyl group as defined above bound to the rest of the molecule through the sulfur atom in the sulfinyl group. The term "lower alkyl sulfonyl" means a lower alkyl group as defined above bound to the rest of the molecule through the sulfur atom in the sulfonyl group.

The term "aryl" means a mono- or bicylic aromatic group, such as phenyl or naphthyl, which is unsubstituted or substituted by conventional substituent groups. Preferred substituents are lower alkyl, lower alkoxy, hydroxy lower alkyl, hydroxy, hydroxyalkoxy, halogen, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, cyano, nitro, perfluoro lower alkyl, alkanoyl, aroyl, aryl alkynyl, lower alkynyl and lower alkanoylamino. Examples of aryl groups that may be used in accordance with this invention are phenyl, p-tolyl, p-methoxyphenyl, p-chlorophenyl, m-hydroxy phenyl, m-methylthiophenyl, 2-methyl-5-nitrophenyl, 2,6-dichlorophenyl, 1-naphthyl and the like.

The term "arylalkyl" means a lower alkyl group as hereinbefore defined in which one or more hydrogen atoms is/are replaced by an aryl or heteroaryl group as herein defined. Any conventional aralkyl may be used in accordance with this invention, such as benzyl and the like.

The term "heteroaryl" means an unsubstituted or substituted 5- or 6-membered monocyclic hetereoaromatic ring or a 9- or 10-membered bicyclic hetereoaromatic ring containing 1, 2, 3 or 4 hetereoatoms which are independently N, S or O. Examples of hetereoaryl rings are pyridine, benzimidazole, indole, imidazole, thiophene, isoquinoline, quinzoline and the like. Substituents as defined above for "aryl" are included in the definition of heteroaryl.

The term "lower alkoxycarbonyl" means a lower alkoxy group bonded via a carbonyl group. Examples of alkoxycarbonyl groups are ethoxycarbonyl and the like.

The term "lower alkylcarbonyloxy" means lower alkylcarbonyloxy groups bonded via an oxygen atom, for example an acetoxy group. This has the same meaning as the term "acyloxy".

The term "lower alkanoyl" means lower alkyl groups bonded via a carbonyl group and embraces in the sense of the foregoing definition groups such as acetyl, propionyl and the like. The term "perfluoro lower alkanoyl" means a perfluoro lower alkyl group (a substituted lower alkyl group where all of the hydrogens are

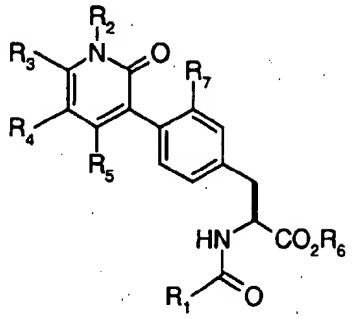
substituted by fluoro, preferably trifluoromethyl or pentafluoroethyl) bonded to the rest of the molecule via a carbonyl group. The term perfluoro lower alkanoylamino" means a perfluoro lower alkanoyl group bonded to the rest of the molecule via an amino group.

The term "lower alkylcarbonylamino" means lower alkylcarbonyl groups bonded to the rest of the molecule via a nitrogen atom, such as acetylamino. The term lower alkylaminocarbonyl" means lower alkyl amino groups bonded to the rest of the molecule via a carbonyl group. The term "arylaminocarbonyl" means aryl groups bonded to an amino group further bonded to the rest of the molecule via a carbonyl group.

The term "aroyl" means a mono- or bicyclic aryl or heteroaryl group bonded to the rest of the molecule via a carbonyl group. Examples of aroyl groups are benzoyl, 3-cyanobenzoyl, 2-naphthoyl, nicotinoyl, and the like.

Pharmaceutically acceptable salts are well known in the art and can be made by conventional methods taking into account the chemical nature of the compound. Examples of pharmaceutically acceptable salts for acidic compounds are alkali metal or alkaline earth metals such as sodium, potassium, calcium, magnesium, basic amines or basic amino acids, ammonium or alkyl ammonium salts. Particularly desirable salts for compounds of this invention are sodium salts, e.g. where R^6 is H. The sodium salt of any acid of this invention is easily obtained from the acid by treatment with sodium hydroxide. For basic compounds, examples are salts of inorganic or organic acids such as hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, citric, formic, fumaric, maleic, acetic, succinic, tartaric, methanesulfonic, and p-toluenesulfonic acid.

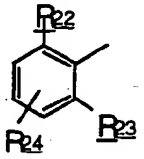
The present invention comprises a compound of formula I:



I

and the pharmaceutically acceptable salts thereof. It also comprises pharmaceutical compositions containing them, their use as medicaments in the treatment of certain diseases, and methods and intermediates for their preparation.

In accordance with the invention, R_1 is a group Y-1, Y-2 or Y-3 as described below: Y-1 is a group of the formula,

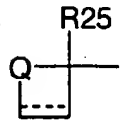


Y-1

wherein: R_{22} and R_{23} are independently hydrogen, lower alkyl, lower alkoxy, cycloalkyl, aryl, arylalkyl, nitro, cyano, lower alkylthio, lower alkylsulfinyl, lower alkyl sulfonyl, lower alkanoyl, halogen, or perfluorolower alkyl and at least one of R_{22} and R_{23} is other than hydrogen, and R_{24} is hydrogen, lower alkyl, lower alkoxy, aryl, nitro, cyano, lower alkyl sulfonyl, or halogen;

Y-2 is a group of the formula Y-2, which is a five or six membered heteroaromatic ring bonded via a carbon atom to the amide carbonyl wherein said ring contains one, two or three heteroatoms selected from the group consisting of N, O and S and one or two atoms of said ring are independently substituted by lower alkyl, cycloalkyl, halogen, cyano, perfluoro lower alkyl, or aryl and at least one of said substituted atoms is adjacent to the carbon atom bonded to the amide carbonyl;

Y-3 is a 3-7 membered ring of the formula:



Y-3

wherein: R_{25} is lower alkyl, unsubstituted or fluorine substituted lower alkenyl, or a group of formula $R_{26}-(CH_2)_e-$,R_{26} is aryl, heteroaryl, azido, cyano, hydroxy, lower alkoxy, lower alkoxycarbonyl, lower alkanoyl, lower alkylthio , lower alkyl sulfonyl,

lower alkyl sulfinyl, perfluoro lower alkanoyl, nitro, or R_{26} is a group of formula $-NR_{28}R_{29}$, wherein R_{28} is hydrogen or lower alkyl, R_{29} is hydrogen, lower alkyl, lower alkoxycarbonyl, lower alkanoyl, aroyl, perfluoro lower alkanoylamino, lower alkyl sulfonyl, lower alkylaminocarbonyl, arylaminocarbonyl, or R_{28} and R_{29}, taken together with the attached nitrogen atom, form a 4, 5 or 6-membered saturated heterocyclic ring optionally containing one additional heteroatom selected from O, S, and N–R_{40}. Q is $-(CH_2)_f O-$, $-(CH_2)_f S-$, $-(CH_2)_f N(R_{27})-$, $-(CH_2)_f-$, R_{27} is H, lower alkyl, aryl, lower alkanoyl, aroyl or lower alkoxycarbonyl, R_{40} is H, lower alkyl, aryl, lower alkanoyl, aroyl or lower alkoxycarbonyl, the carbon atoms in the ring are unsubstituted or substituted by lower alkyl or halogen, e is an integer from 0 to 4, and f is an integer from 0 to 3;

R_2 is hydrogen, lower alkyl, substituted lower alkyl, aryl, or aryl lower alkyl,

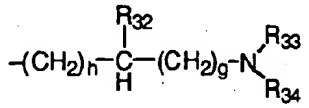
R_3 is hydrogen, halogen, lower alkyl, or aryl, and may also include trifluoromethyl,

R_4 is hydrogen, halogen, lower alkyl, or aryl,

R_5 is hydrogen, lower alkyl, lower alkoxy, trifluoromethyl, or OH,

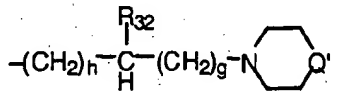
R_6 is hydrogen, lower alkyl, lower alkylcarbonyloxy lower alkyl,

or R_6 is a group of formula P-3:



P-3

wherein: R_{32} is hydrogen or lower alkyl R_{33} is hydrogen, lower alkyl, aryl, R_{34} is hydrogen or lower alkyl, h is an integer from 0 to 2, g is an integer from 0 to 2, the sum of h and g is 1 to 3; or R_6 is a group of formula P-4:



P-4

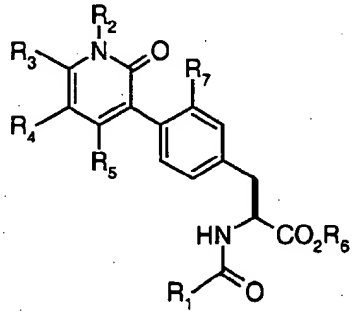
wherein: R_{32}, g, and h are as previously defined, Q' is O, S, $-(CH_2)_j-$, or a group of the formula N-R_{35}, R_{35} is hydrogen, lower alkyl, lower alkanoyl, lower alkoxycarbonyl, j is 0, 1 or 2, R_7 is hydrogen, chloro, lower alkoxy, or lower alkyl.

Preferably Q is $-(CH_2)_f O-$, $-(CH_2)_f S-$, or $-(CH_2)_f-$ (Formula 1a). It is also preferred in compounds of formula I or Formula 1a that R_5 is hydrogen, lower alkyl, or trifluoromethyl (Formula 1b).

The compounds of the invention can exist as stereoisomers and diastereomers, all of which are encompassed within the scope of the present invention.

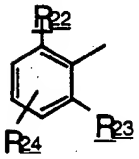
In a first preferred embodiment of the compound of formula I, Formula 1a, or Formula 1b, R_2 is hydrogen, lower alkyl, or aryl lower alkyl, R_3 is hydrogen, lower alkyl, or trifluoromethyl, preferably hydrogen, R_4 is hydrogen or halogen, preferably halogen, R_5 is hydrogen, lower alkyl, trifluoromethyl and may in addition be lower alkoxy, but is preferably hydrogen, R_6 is hydrogen or lower alkyl, and R_7 is hydrogen, chloro, lower alkoxy, or lower alkyl.

A further preferred embodiment of the first preferred embodiment of the present invention is a compound of the formula I, 1a, or 1b:



I

wherein R_1 is a group Y-1

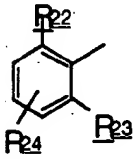


Y-1

wherein R_{22} and R_{23} are independently hydrogen, lower alkyl, lower alkoxy, cycloalkyl, aryl, arylalkyl, nitro, cyano, lower alkylthio, lower alkylsulfinyl, lower alkyl sulfonyl, lower alkanoyl, halogen, or perfluorolower alkyl and at least one of R_{22} and R_{23} is other than hydrogen, and R_{24} is hydrogen, lower alkyl, lower alkoxy, aryl, nitro, cyano, lower alkyl sulfonyl, or halogen, more particular R_{22} and R_{23} are independently lower alkyl or halogen and R_{24} is hydrogen or lower alkoxy; or wherein R_{22} and R_{23} are independently hydrogen, lower alkyl or halogen and R_{24} is hydrogen, lower alkyl or lower alkoxy, especially hydrogen. In such compounds, it is preferred that R_2 is hydrogen, lower alkyl or aryl lower alkyl, especially aryl-

lower alkyl. Moreover, a such compounds it is preferred that R_3 is hydrogen; R_4 is hydrogen, or halogen, or may in addition be lower alkyl (but preferably is halogen); R_5 is hydrogen, lower alkyl, or trifluoromethyl, or may in addition be lower alkoxy (but preferably is hydrogen); R_6 is hydrogen or lower alkyl; and R_7 is hydrogen, chloro, lower alkoxy, or lower alkyl.

A more preferred embodiment of the present invention is a compound of the formula I, Formula 1a, or Formula 1b above wherein R_1 is a group Y-1



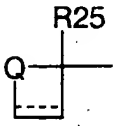
Y-1

wherein R22 and R23 are independently hydrogen, lower alkyl or halogen, especially lower alkyl or halogen; R24 is hydrogen, lower alkyl or lower alkoxy, especially hydrogen. In such compounds, it is preferred that R_2 is hydrogen, lower alkyl or aryl lower alkyl;R_3 is hydrogen; R_4 is hydrogen or halogen, R_5 is hydrogen, or lower alkyl, R_6 is hydrogen or lower alkyl; and R_7 is hydrogen, chloro, lower alkoxy, or lower alkyl. In particularly preferred compounds of this more preferred embodiment R22 and R23 are independently hydrogen, lower alkyl or halogen, R24 is hydrogen or lower alkoxy, and R_2 is aryl lower alkyl. Alternatively, in such compounds, it is preferred that R_2 is hydrogen, lower alkyl or aryl lower alkyl; R_3 is hydrogen; R_4 is hydrogen, or halogen, or may in addition be lower alkyl (but preferably is halogen); R_5 is hydrogen, lower alkyl, or trifluoromethyl, or may in addition be lower alkoxy (but preferably is hydrogen); R_6 is hydrogen or lower alkyl; and R_7 is hydrogen, chloro, lower alkoxy, or lower alkyl.

Another preferred embodiment of the present invention is a compound of the formula I, Formula 1a, or Formula 1b above, especially of the first preferred embodiment, wherein R_1 is a five or six membered heteroaromatic ring bonded via a carbon atom to the amide carbonyl wherein said ring contains one, two or three heteroatoms selected from the group consisting of N, O and S and one or two atoms of said ring are independently substituted by lower alkyl, cycloalkyl, halogen, cyano, perfluoro lower alkyl, or aryl and at least one of said substituted atoms is adjacent to the carbon atom bonded to the amide carbonyl. In such compounds, it

is particularly preferred that R_2 is hydrogen, lower alkyl or aryl lower alkyl; R_3 is hydrogen; R_4 is hydrogen or halogen (preferably halogen); R_5 is hydrogen, trifluoromethyl or lower alkyl (preferably hydrogen); R_6 is hydrogen or lower alkyl; and R_7 is hydrogen, chloro, lower alkoxy, or lower alkyl. Alternatively, in such compounds, it is preferred that R_2 is hydrogen, lower alkyl or aryl lower alkyl; R_3 is hydrogen; R_4 is hydrogen, or halogen, or may in addition be lower alkyl (but preferably is halogen); R_5 is hydrogen, lower alkyl, or trifluoromethyl, or may in addition be lower alkoxy (but preferably is hydrogen); R_6 is hydrogen or lower alkyl; and R_7 is hydrogen, chloro, lower alkoxy, or lower alkyl.

Another preferred embodiment of the present invention is a compound of the formula I, Formula 1a, or Formula 1b above wherein R_1 is a group of the formula Y-3 which is a 3-7 membered ring of the formula:

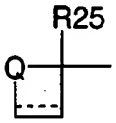


Y-3

wherein R_{25} is lower alkyl, unsubstituted or fluorine substituted lower alkenyl, or a group of formula $R_{26}-(CH_2)_e-$, R_{26} is aryl, heteroaryl, azido, cyano, hydroxy, lower alkoxy, lower alkoxycarbonyl, lower alkanoyl, lower alkylthio , lower alkyl sulfonyl, lower alkyl sulfinyl, perfluoro lower alkanoyl, nitro, or R_{26} is a group of formula $-NR_{28}R_{29}$, wherein R_{28} is hydrogen or lower alkyl, R_{29} is hydrogen, lower alkyl, lower alkoxycarbonyl, lower alkanoyl, aroyl, perfluoro lower alkanoylamino, lower alkyl sulfonyl, lower alkylaminocarbonyl, arylaminocarbonyl; or R_{28} and R_{29}, taken together with the attached nitrogen atom, form a 4, 5 or 6-membered saturated heterocyclic ring optionally containing one additional heteroatom selected from O, S, and $N-R_{40}$. Q is $-(CH_2)_f O-$, $-(CH_2)_f S-$, $-(CH_2)_f N(R_{27})-$, $-(CH_2)_f-$, R_{27} is H, lower alkyl, aryl, lower alkanoyl, aroyl or lower alkoxycarbonyl, R_{40} is H, lower alkyl, aryl, lower alkanoyl, aroyl or lower alkoxycarbonyl, the carbon atoms in the ring are unsubstituted or substituted by lower alkyl or halogen, e is an integer from 0 to 4, and f is an integer from 0 to 3. In such compounds, it is particularly preferred that R_2 is hydrogen, lower alkyl or aryl lower alkyl; R_3 is hydrogen, lower alkyl or trifluoromethyl; R_4 is hydrogen or halogen (preferably halogen); R_5 is hydrogen, trifluoromethyl, or lower alkyl (preferably hydrogen); R_6 is hydrogen or lower alkyl; and R_7 is hydrogen, chloro, lower alkoxy, or lower alkyl.

Alternatively, in such compounds, it is preferred that R_2 is hydrogen, lower alkyl or aryl lower alkyl; R_3 is hydrogen; R_4 is hydrogen, or halogen, or may in addition be lower alkyl (but preferably is halogen); R_5 is hydrogen, lower alkyl, or trifluoromethyl), or may in addition be lower alkoxy (but preferably is hydrogen); R_6 is hydrogen or lower alkyl; and R_7 is hydrogen, chloro, lower alkoxy, or lower alkyl.

A more preferred embodiment of the present invention is a compound of formula I, Formula 1a, or Formula 1b above, especially of the first preferred embodiment, wherein R_1 is a group of the formula Y-3 as defined above, more particular wherein it is a 3-7 membered ring of the formula:



Y-3

wherein R_{25} a group of formula $R_{26}-(CH_2)_e-$, wherein R_{26} is lower alkoxy, Q is $-(CH_2)_f-$, e is an integer from 0 to 4 and f is an integer from 0 to 3; Such compounds are especially preferred where R2 is hydrogen, lower alkyl, substituted lower alkyl, aryl, or aryl lower alkyl, especially aryl lower alkyl. Such compounds are also preferred when R_2 is lower alkyl or aryl lower alkyl; R_3 is hydrogen; R_4 is hydrogen or halogen; R_5 is hydrogen; R_6 is hydrogen or lower alkyl; and R_7 is hydrogen, chloro, lower alkoxy, or lower alkyl. Alternatively, in such compounds, it is preferred that R_2 is hydrogen, lower alkyl or aryl lower alkyl; R_3 is hydrogen; R_4 is hydrogen, or halogen, or may in addition be lower alkyl (but preferably is halogen); R_5 is hydrogen, lower alkyl, or trifluoromethyl), or may in addition be lower alkoxy (but preferably is hydrogen); R_6 is hydrogen or lower alkyl; and R_7 is hydrogen, chloro, lower alkoxy, or lower alkyl.

In any compound of this invention of formula I, Formula 1a, or Formula 1b, R_1 may be a group of formula Y-1 or a group of formula Y-3; R_2 may be hydrogen, lower alkyl or aryl lower alkyl, preferably lower alkyl, in particular methyl, or aryl lower alkyl, in particular benzyl, R_3 may be hydrogen, lower alkyl, or trifluoromethyl, preferably hydrogen or lower alkyl; R_4 may be hydrogen or halogen; R_5 may be hydrogen, lower alkyl, or trifluoromethyl; R_6 may be hydrogen, lower alkyl, lower alkylcarbonyloxy lower alkyl, or a group of formula P-3 and may

in addition be a group of formula P-4; and R_7 may be lower alkyl or hydrogen, preferably hydrogen.

In any compound of this invention of formula I, Formula 1a, Formula 1b, or the preferred compounds described in the paragraph immediately above, the groups within Y-1 and Y-3 may be specifically selected as follows: R_{22} and R_{23} are hydrogen, halogen, lower alkyl, R_{24} is hydrogen or lower alkoxy, R_{25} is a group of formula $R_{26}-(CH_2)_e-$, wherein R_{26} is lower alkoxy, Q is $-(CH_2)_f-$, e is an integer from 0 to 4 and f is an integer from 0 to 3, and/or where R_2 is lower alkyl, R_4 is hydrogen, and R^3 and R_5 are lower alkyl or trifluoromethyl, and R_6 is hydrogen, lower alkyl, or lower alkylcarbonyloxy lower alkyl, or a group of formula P-3 preferably where R_{32} is hydrogen; R_{33} and R_{34} are lower alkyl; one of g and h is 1 and the other is 0. In such compounds, preferably R_6 and R_7 are hydrogen, and/or R_2 is lower alkyl; R_3 is hydrogen; R_4 is hydrogen or halogen; and R_5 is hydrogen or lower alkyl, and preferably R_{22} and R_{23} are lower alkyl or halogen, especially halogen, and R_{24} is hydrogen, or R_{22} and R_{23} are hydrogen or halogen, and R_{24} is hydrogen or lower alkoxy, preferably hydrogen or R_1 is Y-3. Particular compounds are

N-[(2,6-dichlorophenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine;

N-[(2-ethyl-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine;

N-[(2-(1-methylethyl)-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine;

N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine;

N-[(2,6-dichlorophenyl)carbonyl]-4-(1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl)-L-phenylalanine; or

N-[(2-chloro-6-methylphenyl)carbonyl]-4-(1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl)-L-phenylalanine.

In other such compounds, R_{22} and R_{23} are preferably halogen, or lower alkyl, R_{24} is hydrogen, or lower alkoxy, R_{25} is a group of formula $R_{26}-(CH_2)_e-$, wherein R_{26} is lower alkoxy, Q is $-(CH_2)_f-$, e is an integer from 0 to 4 and f is an

integer from 0 to 3, particularly N-[[1-(2-methoxyethyl)cyclopently]carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine, and/or R_2 is aryl lower alkyl; R_3 is hydrogen, R_4 is halogen, and R_5, R_6 and R_7 are hydrogen. It is also preferred that R_1 be Y-1.

In a particularly preferred compound of formula I, Formula 1a, or Formula 1b, R_1 is a group of formula Y-1 or a group of formula Y-3; R_2 is lower alkyl or aryl lower alkyl; R_3 is hydrogen, lower alkyl, or trifluoromethyl; R_4 is hydrogen or halogen; R_5 is hydrogen, lower alkyl, or trifluoromethyl; R_6 is hydrogen, lower alkyl, lower alkylcarbonyloxy lower alkyl, or a group of formula P-3; and R_7 is hydrogen (Formula A)

In a preferred compound of Formula A, the groups within Y-1 and Y-3 may be specifically selected as follows: R_{22} and R_{23} are hydrogen, halogen, or lower alkyl, R_{24} is hydrogen, or lower alkoxy, R_{25} is a group of formula $R_{26}-(CH_2)_e-$, wherein R_{26} is lower alkoxy, Q is $-(CH_2)_f-$, e is an integer from 0 to 4 and f is an integer from 0 to 3 (Formula A-1).

In a preferred compound of Formula A-1, R_2 is lower alkyl, R_4 is hydrogen, and R_3 and R_5 are lower alkyl or trifluoromethyl (Formula A-1a). In one embodiment of Formula A-1a, R_6 is hydrogen. In this embodiment, R_1 may be Y-1, especially where R_{22} and R_{23} are halogen or lower alkyl, or R_1 may be Y-3. In other embodiments of Formula A-1a, R_6 is lower alkyl, especially methyl, or is lower alkylcarbonyloxy lower alkyl, especially 1-(acetoxy)ethyl, or is a group of formula P-3 wherein R_{32} is hydrogen; R_{33} and R_{34} are lower alkyl, especially methyl or ethyl; one of g and h is 1 and the other is 0.

Where R_6 is lower alkyl, particular compounds are

N-[(2,6-dichlorophenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine ethyl ester;

N-[(2,6-dichlorophenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine ethyl ester;

N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine ethyl ester; or

N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine ethyl ester.

Where R_6 is lower alkylcarbonyloxy-lower alkyl, particular compounds are

N-[(2,6-dichlorophenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 1-(acetoxy)ethyl ester;

N-[(2,6-dichlorophenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 1-(acetoxy)ethyl ester;

N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 1-(acetoxy)ethyl ester; or

N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 1-(acetoxy)ethyl ester.

Where R6 is P-3, particular compounds are

N-[(2,6-dichlorophenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 2-[(N,N-diethyl)amino]ethyl ester;

N-[(2,6-dichlorophenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 2-[(N,N-diethyl)amino]ethyl ester;

N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 2-[(N,N-diethyl)amino]ethyl ester; or

N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 2-[(N,N-diethyl)amino]ethyl ester.

In another preferred compound of Formula A-1, R_6 is hydrogen. It is preferred that R_2 is lower alkyl; R_3 is hydrogen; R_4 is hydrogen or halogen; and R_5 is hydrogen or lower alkyl (Formula A-1b). In one embodiment of Formula A-1b, R_1 is Y-1. Preferably R_{22} and $R_{23}$are lower alkyl or halogen, and R_{24} is hydrogen, or R_{22} and R_{23} are halogen, and R_{24} is hydrogen, especially

N-[(2-chloro-6-methylphenyl)carbonyl]-4-(5-chloro-1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine;

N-[(2-chloro-6-methylphenyl)carbonyl]-4-(1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine;

N-[(2-chloro-6-methylphenyl)carbonyl]-4-(1,4-dimethyl-2-oxo-3-pyridinyl)-L-phenylalanine; or

N-[(2,6-dichlorophenyl)carbonyl]-4-(1,4-dimethyl-2-oxo-3-pyridinyl)-L-phenylalanine,

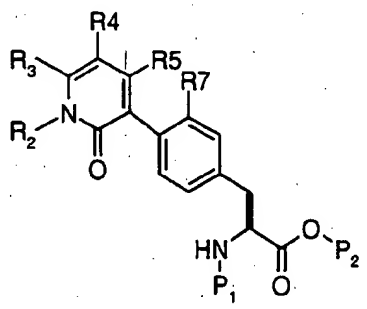
or R_{22} and R_{24} are hydrogen or halogen, and R_{23} is lower alkoxy. In another embodiment of Formula A-1b, R_1 is Y-3, especially 4-(5-chloro-1-methyl-2-oxo-3-pyridinyl)-N-[[1-(2-methoxyethyl)cyclopentyl]carbonyl]-L-phenylalanine.

In another preferred compound of Formula A, wherein R^1 is Y-1 wherein R_{22} and R_{23} are halogen, or lower alkyl, R_{24} is hydrogen or lower alkoxy or wherein R^1 is Y-3 wherein R_{25} is a group of formula $R_{26}-(CH_2)_e-$, wherein R_{26} is lower alkoxy, Q is $-(CH_2)_f-$, e is an integer from 0 to 4 and f is an integer from 0 to 3. Preferably R_2 is aryl lower alkyl; R_3 is hydrogen, R_4 is halogen, and R_5, R_6 and R_7 are hydrogen. Preferably, R_1 be Y-1, especially

4-(1-Benzyl-5-chloro-2-oxo-3-pyridinyl)-N-[(2-chloro-6-methylphenyl)-carbonyl]-L-phenylalanine; or

4-(1-Benzyl-5-chloro-2-oxo-3-pyridinyl)- N-[[1-(2-methoxyethyl)-cyclopentyl]carbonyl]-L-phenylalanine.

In another aspect the present invention relates to compounds of formula II



II

wherein R^2-R^5 and R^7 are as defined in formula I and P_1 and P_2 each are a protecting group. More particular, P_1 is a standard nitrogen protecting group such as tert.butyloxycarbonyl (Boc) or the carbobenzyloxy group and P_2 is a standard carboxy protecting group such as lower alkyl or substituted lower alkyl. These compounds are useful intermediates in the preparation of the compounds of formula I.

The compounds of the invention inhibit the binding of VCAM-1 and fibronectin to VLA-4 on circulating lymphocytes, eosinophils, basophils, and

monocytes ("VLA-4-expressing cells"). The binding of VCAM-1 and fibronectin to VLA-4 on such cells is known to be implicated in certain disease states, such as rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, and particularly in the binding of eosinophils to airway endothelium which contributes to the cause of the lung inflammation which occurs in asthma. Thus, the compounds of the present invention would be useful for the treatment of asthma.

On the basis of their capability of inhibiting binding of VCAM-1 and fibronectin to VLA-4 on circulating lymphocytes, eosinophils, basophils, and monocytes, the compounds of the invention can be used as medicament or a pharmaceutical composition, respectively, especially for the treatment of disorders which are known to be associated with such binding. Examples of such disorders are rheumatoid arthritis, multiple sclerosis, asthma, and inflammatory bowel disease. The compounds of the invention are preferably used in the treatment of diseases which involve pulmonary inflammation, such as asthma. The pulmonary inflammation which occurs in asthma is related to the activation and lung infiltration of eosinophils, monocytes and lymphocytes which have been activated by some asthma-triggering event or substance.

Furthermore, compounds of the invention also inhibit the binding of VCAM-1 and MadCAM to the cellular receptor alpha4-beta7, also known as LPAM, which is expressed on lymphocytes, eosinophiles and T-cells. While the precise role of alpha4-beta7 interaction with various ligands in inflammatory conditions such as asthma is not completely understood, compounds of the invention which inhibit both alpha4-beta1 and alpha4-beta7 receptor binding are particularly effective in animal models of asthma. Furthermore work with monoclonal antibodies to alpha4-beta7 indicate that compounds which inhibit alpha4-beta7 binding to MadCAM or VCAM are useful for the treatment of inflammatory bowel disease. They would also be useful in the treatment of other diseases in which such binding is implicated as a cause of disease damage or symptoms.

The compounds of the invention can be administered orally, rectally, or parentally, e.g., intravenously, intramuscularly, subcutaneously, intrathecally or transdermally; or sublingually, or as opthalmalogical preparations, or as an aerosol

in the case of pulmonary inflammation. Capsules, tablets, suspensions or solutions for oral administration, suppositories, injection solutions, eye drops, salves or spray solutions are examples of administration forms.

Intravenous, intramuscular, oral or inhalation administration is a preferred form of use. The dosages in which the compounds of the invention are administered in effective amounts depending on the nature of the specific active ingredient, the age and the requirements of the patient and the mode of administration. Dosages may be determined by any conventional means, e.g., by dose-limiting clinical trials. Thus, the invention further comprises a method of treating a host suffering from a disease in which VCAM-1 or fibronectin binding to VLA-4-expressing cells is a causative factor in the disease symptoms or damage by administering an amount of a compound of the invention sufficient to inhibit VCAM-1 or fibronectin binding to VLA-4-expressing cells so that said symptoms or said damage is reduced. In general, dosages of about 0.1-100 mg/kg body weight per day are preferred, with dosages of 1-25 mg/kg per day being particularly preferred, and dosages of 1-10 mg/kg body weight per day being espeically preferred.

In another aspect the invention further relates to medicaments or pharmaceutical compositions comprising a pharmaceutically effective amount of a compound of the invention, including pharmaceutical acceptable salts thereof, and a pharmaceutically acceptable carrier. It also relates to a process for the preparation of a pharmaceutical composition which process comprises bringing a compound according to the present invention including a pharmaceutically acceptable salt thereof, and a compatible pharmaceutical carrier into a galenical administration form. Such compositions may be formulated by any conventional means. Tablets or granulates can contain a series of binders, fillers, carriers or diluents. Liquid compositions can be, for example, in the form of a sterile water-miscible solution. Capsules can contain a filler or thickener in addition to the active ingredient. Furthermore, flavour-improving additives as well as substances usually used as preserving, stabilizing, moisture-retaining and emulsifying agents as well as salts for varying the osmotic pressure, buffers and other additives can also be present.

The previously mentioned carrier materials and diluents can comprise any conventional pharmaceutically acceptable organic or inorganic substances, e.g.,

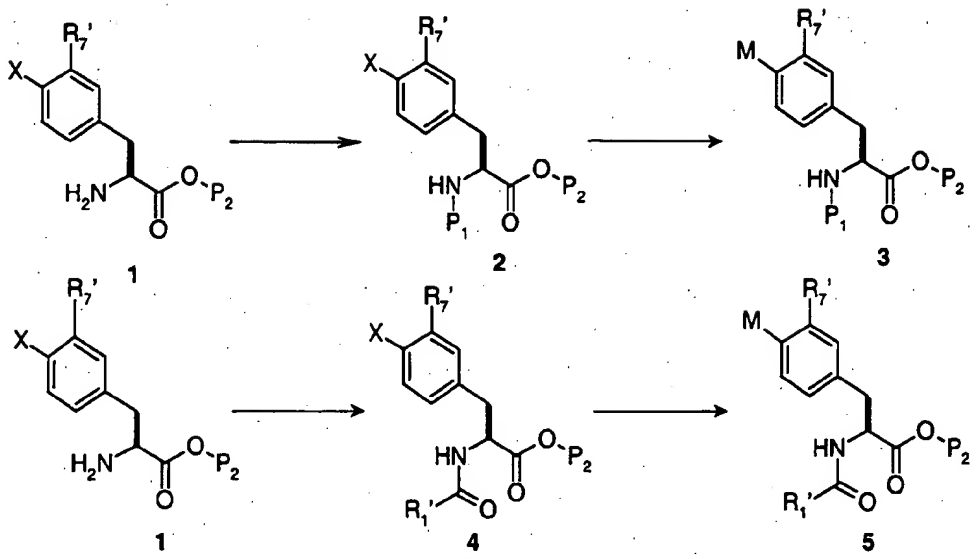
water, gelatine, lactose, starch, magnesium stearate, talc, gum arabic, polyalkylene glycols and the like.

Oral unit dosage forms, such as tablets and capsules, preferably contain from 25 mg to 1000 mg of a compound of the invention.

Generally the compounds of the present invention can be prepared from suitable phenylalanine derivatives via a palladium catalyzed reaction with a 3-halo-2-pyridone.

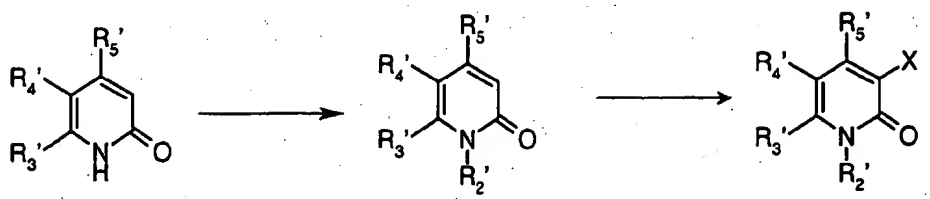
As shown in Reaction Scheme 1, a 4-iodo- or 4-bromophenylalanine derivative such as 1, is converted into a protected phenylalanine derivative 2 in which R_7' is hydrogen, chloro, lower alkyl or lower alkoxy, P_1 is a standard nitrogen protecting group such as a Boc, or carbobenzyloxy group and P_2 is lower alkyl or substituted lower alkyl selected appropriately to serve as a protecting group or an element of a prodrug. The group P_2 can be introduced by conventional means familiar to those who practice peptide chemistry. The order of the addition of P_1 and P_2 is not critical and will depend on the particular choice of reagents. A discussion of the use and introduction of protecting groups is provided in Theodora W. Greene and Peter G. M. Wuts., *Protecting Groups in Organic Synthesis*, Wiley Interscience, New York, 1991. Alternatively, a compound of formula 1 may be converted to a compound of formula 4, in which R_1' represents a component of an acyl group of the invention. A convenient method is to introduce the ester group P_2 first, followed by a coupling reaction of the free amine using conventional peptide coupling reagents, for example HBTU in the presence of a tertiary amine base such as diethylisopropylamine. Again, the particular choice of reagents may dictate altering the sequence of the introduction of R_1' and P_2. Conversion of compounds of formula 2 or 4 to derivatives 3 or 5, in which M represents a substituted tin or boron atom, can be effected by treatment with a suitable species, for example hexamethylditin, hexabutylditin or a tetraalkoxydiboron in the presence of a source of palladium zero. The methodology is outlined and referenced in F. Diederich and P. J. Stang, ed, *Metal Catalyzed Cross Coupling Reactions*, Wiley-VCH, Weinheim, Germany, 1998.

Reaction Scheme 1.



Substituted pyridones of formula 6 wherein $R_{3'}$, $R_{4'}$, and $R_{5'}$ are hydrogen, lower alkyl, perfluorolower alkyl, halogen, aryl, hydroxy, or lower alkoxy are commercially available or prepared following the literature methods (for example, discussion of some of these known methods are found in: P. Wirth, et al., Ger. Offen. 28 17 293, Aug. 12, 1979, Masaru Hojo, et al. Chem. Lett. 1976, 499-502, Robert W. Lang, et al. Helvetica Chimica Acta, 1988, *71*, 596-601). Compounds of formula 7 wherein $R_{2'}$ is lower alkyl or aryl lower alkyl, are obtained by alkylation of compounds of formula 6 by treatment with an alkylating agents such as iodomethane, benzylbromide in the presence of a base such as potassium carbonate and optionally, a phase transfer catalyst. For less reactive alkylating agents, it may be necessary to use a stronger base such as an alkali metal hydroxide and to heat the reaction mixture. Compounds of formula 7 as defined above may be halogenated in the 3-position by treatment with conventional halogenating reagents such as bromine, N-iodosuccinimide or N-bromosuccinimide in a suitable solvent such as glacial acetic acid or aqueous acetic acid to give halopyridones of formula 8, X = Br or I, $R_{2'}$ is independently hydrogen, lower alkyl, substituted lower alkyl, or aryl lower alkyl, $R_{3'}$ and $R_{5'}$ are hydrogen, lower alkyl or perfluorolower alkyl. Treatment with excess halogenating agent leads to compounds of structure 8 with $R_{4'}$ = halogen. For compounds of formula 8 with $R_{2'}$ = aryl, it is convenient to start with N-aryl pyridones which are known compounds or to introduce an aryl moiety for example an using an Ullmann coupling reaction as described by Masakatusu, et al., Chem. Pharm. Bull. 1997, *45*, 719.

Reaction Scheme 2.

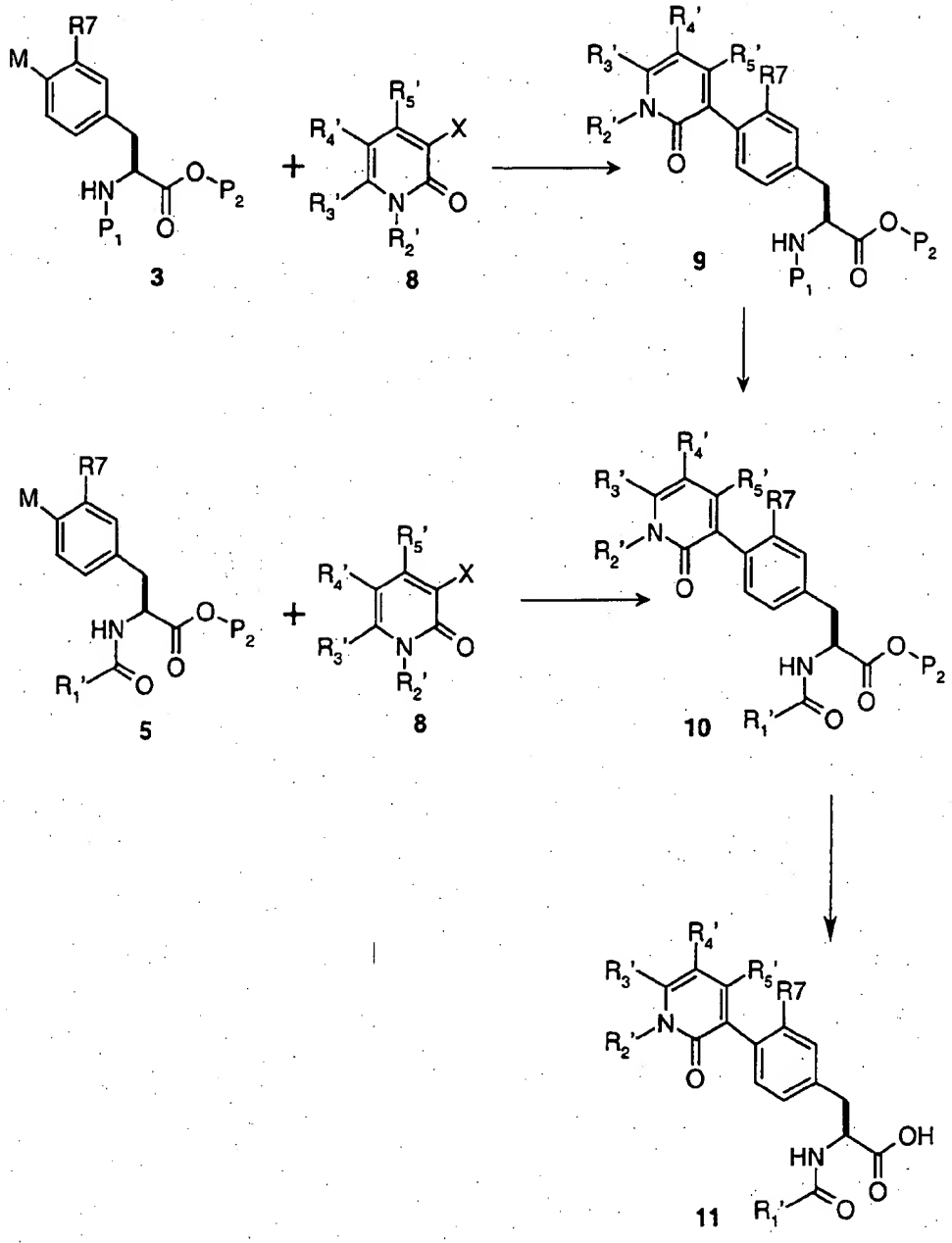


6 7 8

As shown in Reaction Scheme 3, the compound of formula 8 can be used in a palladium catalyzed coupling reaction with a phenylalanine derivative of formula 3 or 5. For example, when M is a substituted tin, treatment of a mixture of 8 and the phenylalanine of formula 3 or 5 with a source of palladium zero such as tetraakis(triphenylphosphine)palladium or bis(triphenylphosphine)palladium dichloride in the presence of an inert solvent such as DMF at a temperature of between room temperature and 100 °C gives a compound of formula 9 or 10. Compounds of structure 9 may be converted into compounds of structure 10 by removal of the protecting group P_1, which may be accomplished by conventional means depending on the selection of P_1. For example, if P_1 is a Boc group, it may be removed by treatment with a strong acid, such as trifluoroacetic acid, optionally in the presence of a solvent such as methylene chloride and a scavenging agent. The resulting free amine may then be acylated with an acid of the formula $R_1'CO_2H$ using convention peptide coupling techniques. For example, by treatment with HBTU in the presence of a tertiary amine base such as diethylisopropylamine in the presence of an aprotic solvent such as DMF to give the compound of structure 10.

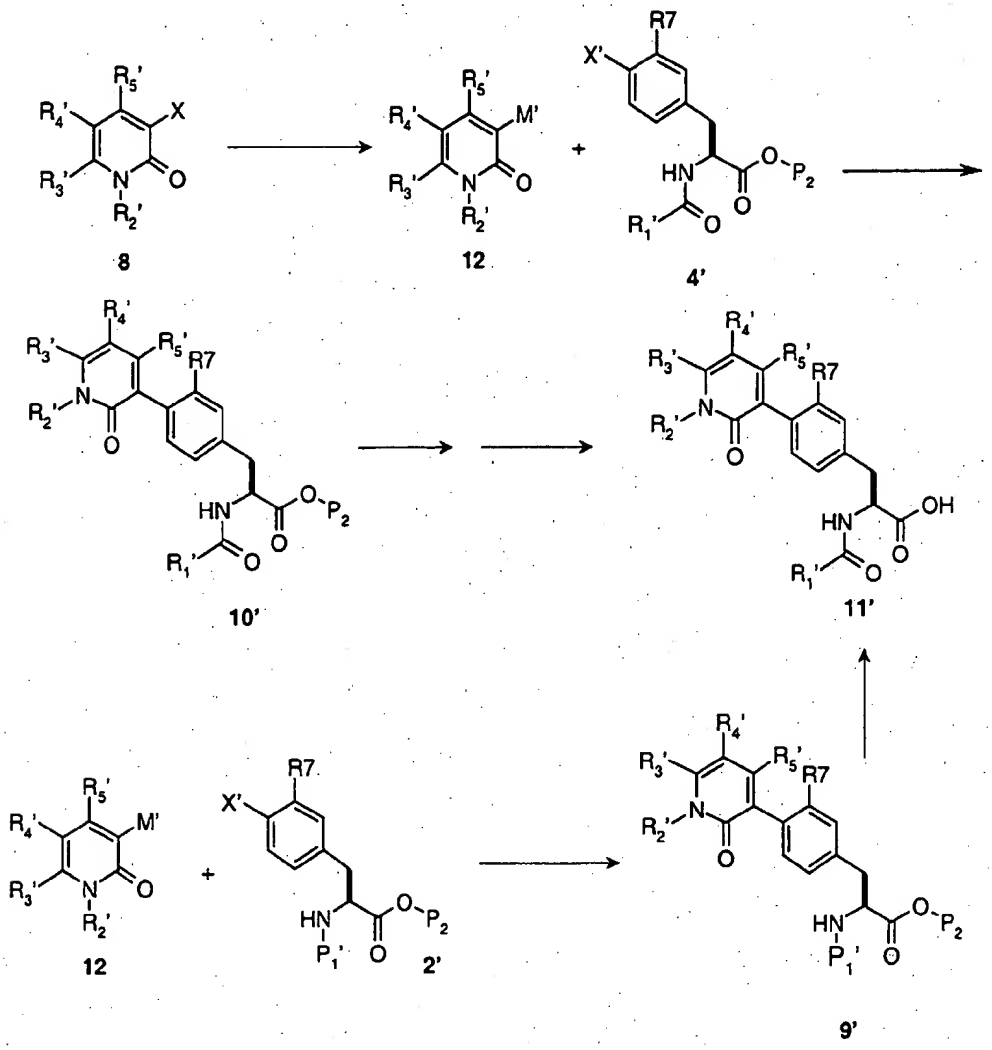
If the free acid 11 is the desired end product, the ester group, P_2 may be removed by conventional means. For example, in the case that P_2 is lower alkyl, for example methyl, it may be removed by treatment with an alkali metal hydroxide, for example lithium hydroxide, in a suitable solvent, for example aqueous THF optionally containing methanol to assist with solubility. If P_2 were a benzyl or substituted benzyl group, it could also be removed by catalytic hydrogenation over a noble metal catalyst, for example palladium on carbon.

Reaction Scheme 3.



Alternatively, as shown in Reaction Scheme 4, a compound of structure 8, wherein X is bromide or iodide, may be converted to a species of formula 12, in which M' represents a substituted tin, boron or zinc atom. In the case of the tin or boron derivatives, in which M' represents a substituted tin or boron atom, the conversion can be effected by treatment with a suitable species, for

Reaction Scheme 4.



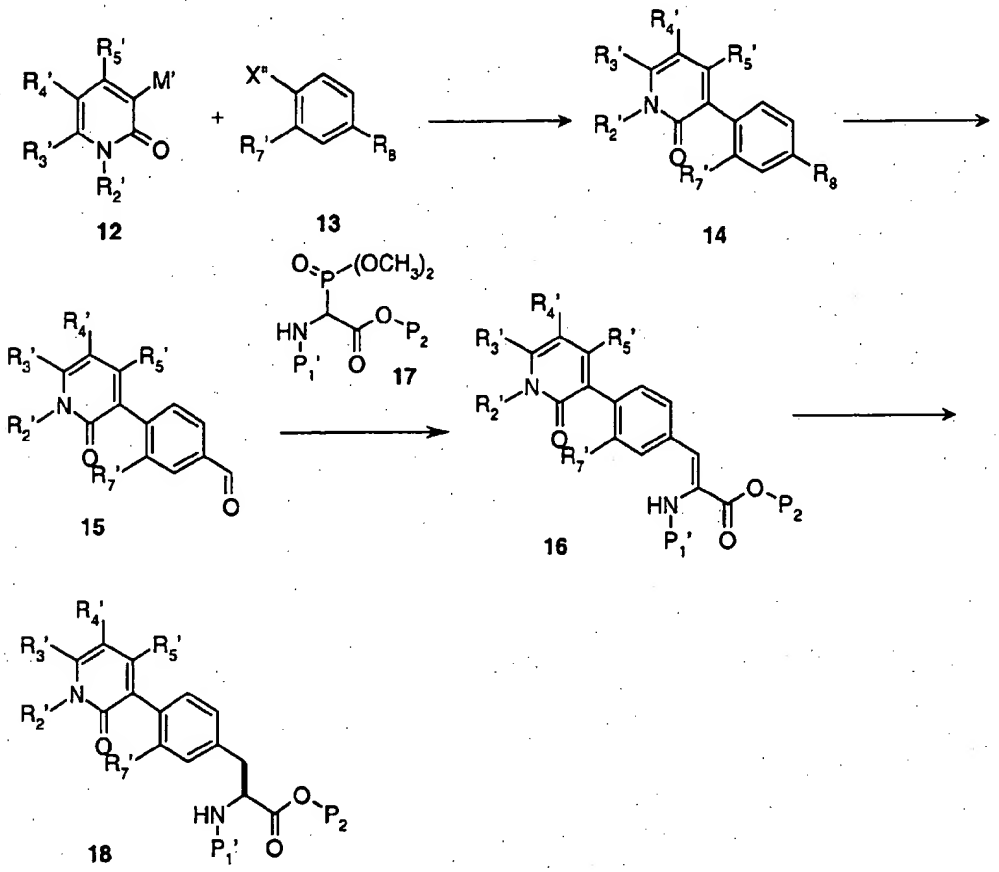
example hexamethylditin, hexabutylditin or a tetraalkoxydiboron in the presence of a source of palladium zero. For the formation of the zinc derivative, 12, M' = Zn(halogen), conversion may be effected by treatment of the compound of formula 8, X = I with a source of activated zinc metal in a suitable inert solvent, for example dimethylacetamide at a temperature of from room temperature to 100 °C until conversion is complete to give a compound of formula 12, M' = Zn(halogen). These compounds of formula 12 can be reacted with a 4-substituted phenylalanine derivative of formula 4' in which X' is iodo, bromo, or trifluoromethylsulfonyloxy in the presence of a source of palladium zero to give a compound of formula 10'. In the case where the ester group represented by P_2 is not part of the targeted compound, it can be removed using ester hydrolysis procedures appropriate to the particular P_2. For example, where P_2 is lower alkyl, for example methyl, it can be

removed by standard base hydrolysis using an alkali metal hydroxide, for example, lithium hydroxide. In a variation on this procedure, it may be desirable to carry a protecting group through the coupling reaction and substitute it at a later time. In this case, a compound of formula 2', in which P_1' is lower alkoxycarbonyl or benzyloxycarbonyl and X' is as defined above, may be coupled with a pyridone of structure 12 to give a compound of structure 9' which in turn may be converted to a compound of the invention using the general procedures noted above in reaction scheme 3.

An alternative route to compounds of this invention, as shown in Reaction Scheme 5, which is particularly applicable to compounds in which R_7' is other than hydrogen, is to build an aldedyde of formula 14. This can be accomplished by reacting a compound of formula 12 with a compound of formula 13, in which R_7' represents lower alkyl or lower alkoxy, and X" represents an iodide, bromide, of trifluoromethylsulfonyloxy moiety and R_8 represents a protected alcohol or an aldehyde. For alcohols, suitable protecting groups include silyl ethers, benzyl ethers. If necessary, aldehydes, may be protected as their acetal derivatives. The compound of formula 12 can be converted to an aldehyde of formula 15 by convertional steps which, when R_8 is an alcohol, would involve protecting group removal, if necessary, followed by oxidation. Any of the common reagents for the selective oxidation of primary benzyl alcohols to aldehydes may be employed, for example, treatment with activated manganese dioxide in an inert solvent. In the case where R_8 represents a protected aldehyde, conversion to an aldehyde of formula 15 can be carried out by a suitable protecting group removal, for example hydrolysis of an acetal with dilute acid. Reaction of 15 to give a dehydroamino acid of formula 16 can be effected by treatment with a Wittig reagent of formula 17 in which P_1' is lower alkoxycarbonyl or benzyloxycarbonyl and P_2 is as defined above. For example treatment of 15 with (±)-N-(benzyloxycarbonyl)-α-phosphonoglycine trimethyl ester in the presence of a suitable base for example tetramethylguanidine leads directly to a dehydroamino acid of formula 16, P_2 = methyl and P_1' = benzyloxycarbonyl. Enantioselective reduction of 16 to the L-amino acid 18 can be effected by use of a number of reducing agents suitable for the purpose, for example, the recently described ethyl-DuPHOS rhodium reagent (Burk, M. J., Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* 1993, *115*, 10125) using essentially the literature procedure. Further conversion of 18 to the

compounds of the invention can be carried out using the general procedures discussed above. Alternatively, the general methods outlined in reaction scheme 5 can be used to prepare compounds of structure 4 or 4' in which R_7' is other than hydrogen. These compounds of structure 4 or 4' can then be employed to prepare compounds of the invention as outlined in reaction schemes 1 to 4.

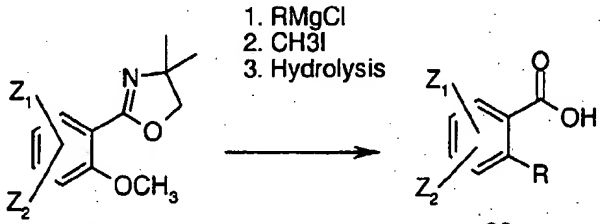
Reaction Scheme 5.



In one embodiment, the N-acyl group, R_1' of structure 11, is derived from a 2-subsituted benzoic acid. Appropriate 2-substituted benzoic acids are either commercially available or can be prepared by conventional means. For example ortho-substituted aryl iodides or triflates may be carbonylated in the presence of carbon monoxide and a suitable palladium catalyst. The preparation of such iodide or triflate intermediates is dependent on the particular substitution pattern desired and they may be obtained by direct iodination or diazotization of an aniline followed by treatment with a source of iodide for example, potassium iodide. Triflates may be derived from the corresponding phenols by conventional means such as by treatment with trifluoromethane sulfonic anhydride in the presence of a

base such as triethylamine or diisopropylethylamine in an inert solvent. As shown in Reaction Scheme 6, one other means of obtaining ortho-substituted benzoic acids involves treatment of an 2-methoxyphenyloxazoline derivative such as compound 19, Z_1 and Z_2 = hydrogen, alkyl, chloro, perfluoro lower alkyl, lower alkoxy with an alkyl Grignard reagent followed by hydrolysis of the oxazoline ring following the general procedure described by Meyers, A. I., Gabel, R., Mihelick, E. D, *J. Org. Chem.* 1978, 43, 1372–1379, to give an acid of formula 20. 2- or 2,6-Disubstituted benzonitriles also serve as convenient precursors to the corresponding benzoic acids. In the case of highly hindered nitriles, for example 2-chloro-6-methylbenzonitrile, conventional hydrolysis under acidic or basic conditions is difficult and better results are obtained by DIBAL reduction to the corresponding benzaldehyde followed by oxidation using a chromium based oxidizing reagent. Other methods are exemplified in Chen, et al., WO 9910312.

Reaction Scheme 6



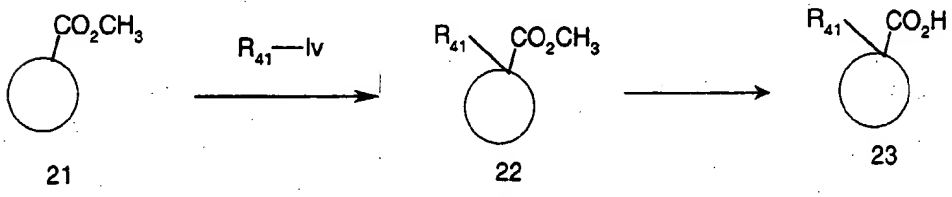
19 20

Referring now to Reaction Scheme 7, cyclic acids of formula 23 are known compounds or can be prepared using standard methodologies. For the preparation of substituted alkyl- or cycloalkylcarboxylic acids, alkylation reactions can be employed using an alkali metal dianion of the acid or monoanion of the corresponding ester. For example, a cycloalkyl carboxylic acid ester of formula 21 can be treated with a strong base, for example, lithium diisopropylamide in an inert solvent, for example THF followed by addition of group R_{41}–Lv wherein R_{41} represents a desired side chain, such as a substituted benzyl, lower alkyl, lower alkoxy alkyl, azidolower alkyl and the like and Lv represents a leaving group such as a bromide, iodide, mesylate or similar group known to participate in ester enolate alkylation reactions. The product ester 22 may be hydrolyzed to the acid 23 using alkali metal hydroxide in a suitable solvent, for example aqueous alcohol. Depending on the nature of R_{41} and the eventual target, the compound 23 may be coupled to an amine such as compound 1 and converted to the target directly or R_{41} may be subject to further manipulation at a suitable point in the synthesis. For

example, if R_{41} is an azido lower alkyl moiety, the azide may be reduced using for example a trialkyl phosphine reagent followed by functionalization of the product amine by alkylation, acylation, sulfonylation and related procedures well known to those skilled in the art. If R_{41} incorporates a leaving group, for example, a terminal bromine atom, this group may be displaced by an appropriate nucleophile, for example, sodium methyl mercaptide to give in this case, a thioether which may be the desired product or can be itself further manipulated, for example by oxidation to a sulfoxide or sulfone using standard reaction conditions. Other nucleophiles which may be employed to produce intermediates leading to compounds of this invention include: sodium cyanide, sodium methoxide, sodium azide, morpholine and others. When R_{41} incorporates a ketal group, this group may be hydrolzyed at a convenient point in the synthesis to provide a keto group. This group in turn may be further manipulated, for example by reduction to an alcohol or conversion to derivative such as an oxime.

Examples of the application of these methods to the synthesis of compounds of formula 23 are provided in Chen, et al. WO 9910313.

Reaction Scheme 7.

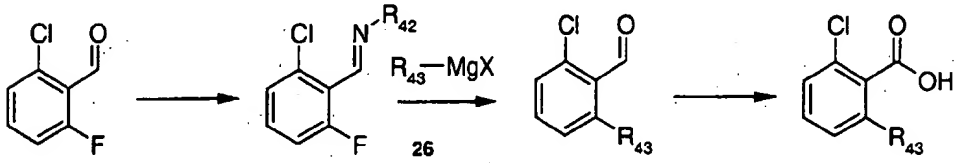


In general, ortho-substituted aromatic acids needed for the preparation of compounds in which R^1 = Y-1 can be prepared as exemplified in Chen, et al., WO9910312.

For the synthesis of 2-chloro-6-alkylbenzoic acids of formula 28, wherein R43 is lower alkyl or cycloalkyl, the procedure described in Reaction Scheme 8 is particularly suitable. Thus a commercially available aldehyde of formula 24 is converted to the imine 25 wherein R42 is lower alkyl, preferably butyl, by treatment with butylamine in an inert, hydrophobic organic solvent, for example heptane. The resulting compound of formula 25 is treated with an excess of a Grignard derivative 26 in an inert solvent, for example THF, followed by acid treatment during the workup to give an aldehyde of formula 27. Oxidation of 27 to an acid of

formula 28 can be carried out by conventional means, for example by treatment of a solution of 27 in a suitable solvent such as aqueous acetonitrile with sodium chlorite and 30% hydrogen peroxide at or below room temperature.

Reaction Scheme 8



24 25 27 28

It may be desirable to prepare prodrug esters of the compounds of this invention for which it would be more convenient to introduce the ester moiety at the end of the synthesis. For this purpose, a variety of common techniques for the formation of esters from carboxylic acids may be employed. Typical methods which may be useful would include, coupling of an alcohol to the carboxylic acid in the presence of acid, for example hydrochloric acid, a procedure commonly known as a Fisher esterification. Alternatively, a diimide mediated coupling between the carboxylic acid and an alcohol may be employed with the optional use of a promoter such as 4,4-dimethylaminopyridine. A typical diimide is dicyclohexylcarbodiimide. Another alternative is to treat the carboxylic acid with a reactive alkyl halide, for example, an alkyl iodide or an acyloxymethyl chloride in the presence of a base, for example sodium bicarbonate and an inert solvent, for example DMF. The particular choice of method will be determined by the nature of the particular combination of carboxylic acid and desired ester moiety and will be apparent to one skilled in the art. Ester groups which may constitute prodrugs may be introduced at any convenient point in the synthesis. For example the group P_2 in formula 1 may represent a desirable prodrug ester and be retained in the final product.

EXAMPLES

The Examples which follow are for purposes of illustration and are not intended to limit the invention in any way.

General Methods: Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Optical rotations were determined with a Perkin-Elmer model 241 polarimeter. ^{1}H-NMR spectra were recorded with Varian XL-200, Mercury 300 and

Unityplus 400 MHz spectrometers, using tetramethylsilane (TMS) as internal standard. Electron impact (EI, 70 ev) and fast atom bombardment (FAB) mass spectra were taken on VG Autospec or VG 70E-HF mass spectrometers. Silica gel used for column chromatography was Mallinkrodt SiliCar 230-400 mesh silica gel for flash chromatography; columns were run under a 0–5 psi head of nitrogen to assist flow. Thin layer chromatograms were run on glass thin layer plates coated with silica gel as supplied by E. Merck (E. Merck # 1.05719) and were visualized by viewing under 254 nm UV light in a view box, by exposure to I_2 vapor, or by spraying with either phosphomolybdic acid (PMA) in aqueous ethanol, or after exposure to Cl_2, with a 4,4'-tetramethyldiaminodiphenylmethane reagent prepared according to E. Von Arx, M. Faupel and M Brugger, *J. Chromatography*, 1976, *120*, 224–228.

Reversed phase high pressure liquid chromatography (RP-HPLC)was carried out using a Rainin HPLC employing a 41.4 x 300 mm, 8 μM, Dynamax™ C-18 column at a flow of 49 mL/min employing a gradient of acetonitrile:water (each containing 0.75% TFA) typically from 5 to 95% acetonitrile over 35-40 min. HPLC conditions are typically described in the format (5-95-35-214); this refers to a linear gradient of from 5% to 95% acetonitrile in water over 35 min while monitoring the effluent with a UV detector at a wavelength of 214 nM.

Methylene chloride (dichloromethane), 2-propanol, DMF, THF, toluene, hexane, ether, and methanol, were Fisher reagent grade and were used without additional purification except as noted, acetonitrile was Fisher or Baker hplc grade and was used as is.

Definitions as used herein:

THF is tetrahydrofuran,
DMF is N,N-dimethylformamide,
DMA is N,N-dimethylacetamide
HOBT is 1-hydroxybenzotriazole,
BOP is [(benzotriazole-1-yl)oxy]tris-(dimethylamino)phosphonium hexafluorophosphate,

HATU is O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate

HBTU is O-benzotriazole-N,N,N',N',-tetramethyluronium hexafluorophosphate,

DIPEA is diisopropylethylamine,

DMAP is 4-(N,N-dimethylamino)pyridine

DPPA is diphenylphosphoryl azide

DPPP is 1,3-bis(diphenylphosphino)propane

DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene

NaH is sodium hydride

brine is saturated aqueous sodium chloride solution

TLC is thin layer chromatography

LDA is lithium diisopropylamide

BOP-Cl is bis(2-oxo-3-oxazolidinyl)phosphinic chloride

NMP is N-methyl pyrrolidinone

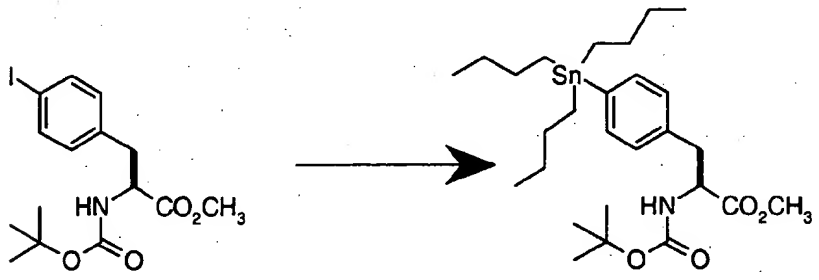
Lawesson's reagent is [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide]

NIS is N-iodosuccinimide.

Silica gel chromatography on Biotage columns refers to use of a flash chromatography system supplied by the Biotage Division of the Dyax Corporation employing prepacked 40g (40s columns), 90g (40m columns) or 800g (75m columns). Elution is carried out with hexane-ethyl acetate mixtures under 10-15 psi nitrogen pressure.

Example 1.

N-[(1,1-dimethylethoxy)carbonyl]-4-[(tributyl)stannyl]-L-phenylalanine methyl ester.

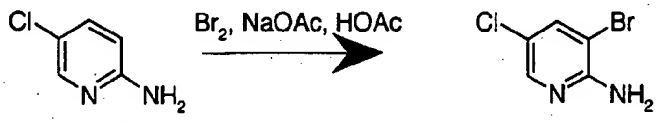


A solution of N-[(1,1-dimethylethoxy)carbonyl]-4-iodo-L-phenylalanine methyl ester (5.3 g, 13 mmol) and hexabutylditin (27.5 mL, 54 mmol) in toluene (50 mL)

was deoxygenated by alternately freezing the mixture in a liquid nitrogen bath under vacuum and thawing under argon (3 x). Tetrakis(triphenylphosphine)-palladium was added (280 mg, 0.22 mmol) and the reaction mixture was heated to reflux for 45 min as the color changed from yellow to black. TLC (1:6 ethyl acetate:hexane) indicated the presence of some starting iodide and an additional portion (140 mg, 0.11 mmol) of the catalyst was added. Reflux was continued for 1 hr. The mixture was allowed to cool and was concentrated. The residue was taken up in hexane (200 mL) and triethylamine (30 mL), stirred for 30 min and was filtered. The filtrate was concentrated and was chromatographed over a dry silica gel column containing 150 g of silica gel and eluting with hexane followed by 1:6 ethyl acetate:hexanes to give N-[(1,1-dimethylethoxy)carbonyl]-4-[(tributyl)stannyl]-L-phenylalanine methyl ester (5.7 g, 77%) as a clear oil. LR(+)LSIMS ($C_{27}H_{47}NO_4Sn$): m/z 1081 (2M-C4H9) 570 (M+H).

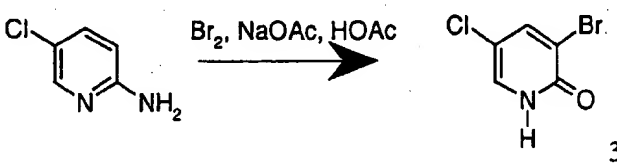
Example 2.

2-Amino-3-bromo-5-chloropyridine



A suspension of 2-amino-5-chloropyridine (5.14 g, 40 mmol) and anhydrous sodium acetate (3.29g, 40 mmol) in acetic acid (25 mL) was mechanically stirred and warmed to a bath temperature of 45 °C. A solution of bromine (2.1 mL, 40 mmol) in acetic acid (2 mL) was added over 1 hour. The resulting orange mixture was cooled to 15 °C and filtered. The solids were taken up in 400 mL of water, the suspension made basic by addition of 1 N NaOH and the suspension extracted with ethyl acetate (5 x 100 mL). The combined extracts were washed with 10 % $NaHSO_3$ (1 x 100 mL) and were dried over $MgSO_4$. Concentration afforded 2-amino-3-bromo-5-chloropyridine (4g, 48%), mp 82-84 °C.

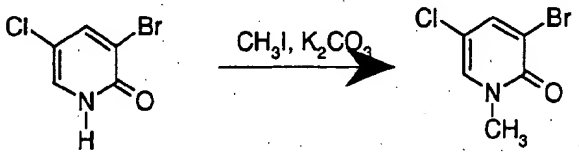
Example 3.



3-Bromo-5-chloro-1H-2-pyridone

A solution of 2-amino-3-bromo-5-chloropyridine (4.0 g, 19.3 mmol) in water (30 mL) and conc. HCl (5.2 mL) was cooled with an ice bath to 0 °C and was treated with a solution of sodium nitrite (1.33 g, 19.3 mmol) in water (12 mL) over 10 min. The mixture was stirred for an additonal 10 min and allowed to warm to room temperature over 48 hr. The mixture was filtered. The solids were washed with water, then with CCl_4 and were dried under vacuum at 50 °C for 3 hr to give 3-bromo-5-chloro-1H-2-pyridone (2.77 g, 69%), mp 173.5-175 °C.

Example 4.

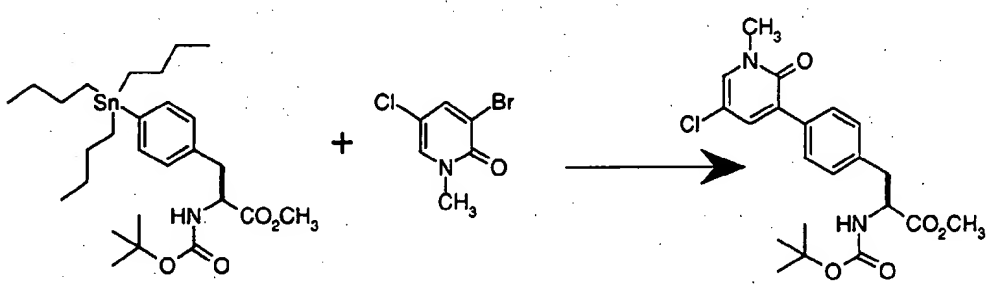


3-Bromo-5-chloro-1-methyl-2-pyridone

A mixture of 3-bromo-5-chloro-1H-2-pyridone (930 mg, 4.46 mmol), potassium carbonate (1.25 g, 9.1 mmol) and iodomethane (2.8 mL, 45 mmol) in 10 mL of DME was heated to reflux for 18 hr. The mixture was filtered hot and concentrated. The residue was recrystallized from ethyl acetate to give 3-bromo-5-chloro-1-methyl-2-pyridone (740 mg, 74%), mp 162-163 °C. HRMS (C6H5BrClNO): Obs. Mass 220.9249. Calcd. Mass 220.9243 (M+H).

Example 5.

4-(5-Chloro-1-methyl-2-oxo-3-pyridinyl)-N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanine methyl ester

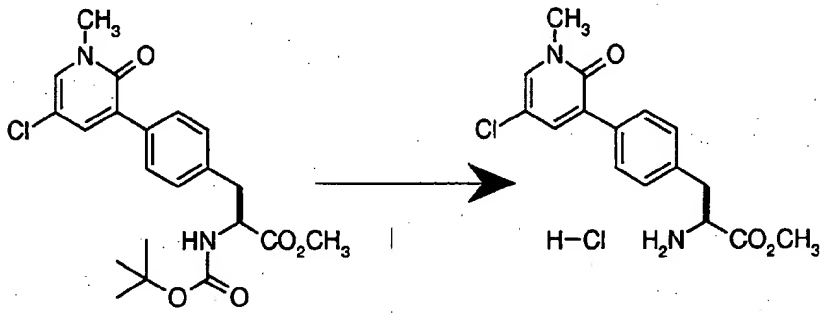


A solution of 3-bromo-5-chloro-1-methyl-2-pyridone (660 mg, 2.97 mmol) and N-[(1,1-dimethylethoxy)carbonyl]-4-[(tributyl)stannyl]-L-phenylalanine methyl ester (1.7 g, 2.99 mmol) in DMF (30 mL) was deoxygenated by alternately freezing the mixture in a liquid nitrogen bath under vacuum and thawing under argon (3 X).

Tetrakis(triphenylphosphine)palladium (140 mg, 0.20 mmol) was added and the mixture was heated to 90 °C for 3 hr as the mixture turned dark. TLC indicated that the reaction was not complete and an additional 140 mg portion of the catalyst was added and heating continued for 4 hr. The mixture was allowed to cool and was diluted with dichloromethane and was filtered through a pad of celite. The filtrate was evaporated to dryness and the residue was dissolved in 1:1 ether:ethyl acetate (60 mL). The solution was washed with water (3 x 10 mL) and brine (1 x 10 mL) and was dried ($MgSO_4$). The residue obtained upon concentration was chromatographed over 150 g of silica gel eluting with 7:3 ethyl acetate:hexane to give 4-(5-chloro-1-methyl-2-oxo-3-pyridinyl)-N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanine methyl ester (670 mg, 54%). LRMS-Electrospray : m/z 863 (2M+Na), 858 (2M+NH4), 443 (M+Na), 438 (M+NH4), 421(M+H).

Example 6.

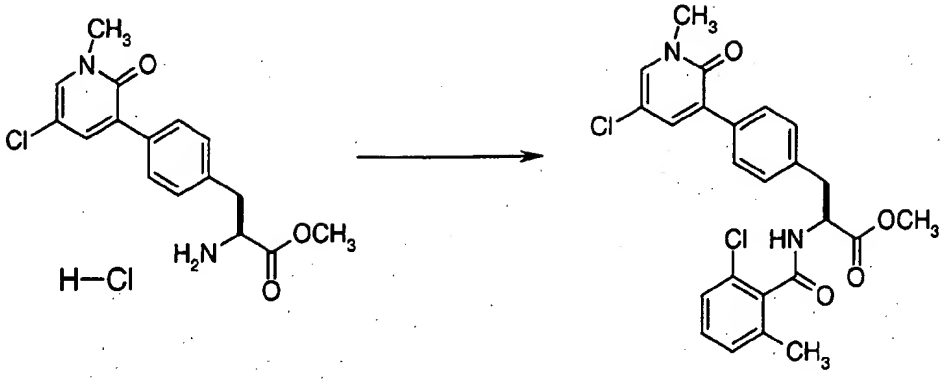
4-(5-chloro-1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester hydrochloride



A solution of 4-(5-chloro-1-methyl-2-oxo-3-pyridinyl)-N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanine methyl ester (210 mg, 0.50 mmol) in 4 N HCl in dioxane (10 mL) was stirred for 1 hr and was concentrated to give 4-(5-chloro-1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester (140 mg) as a white powder. LR(+)LSIMS : m/z 641 (2M+H), 321 (M+H).

Example 7.

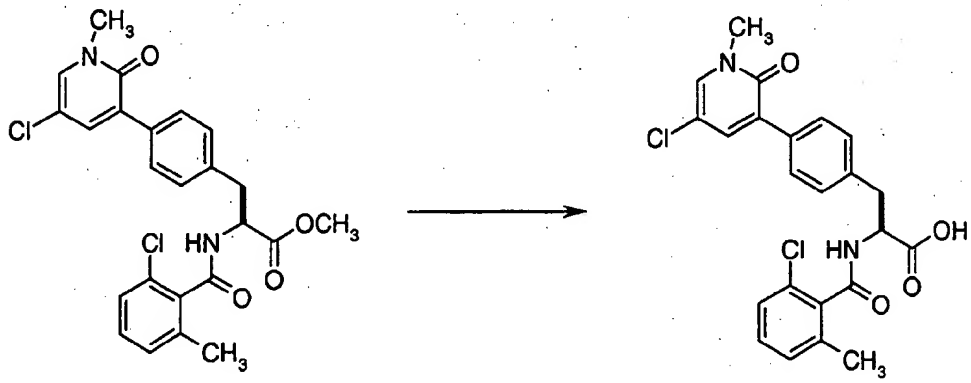
N-[(2-Chloro-6-methylphenyl)carbonyl]-4-(5-chloro-1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester



A solution of 4-(5-chloro-1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester hydrochloride (89.5 mg, 0.25 mmol), 2-chloro-6-methylbenzoic acid (47 mg, 0.28 mmol), DIEA (175 µL, 1.0 mmol) and HBTU (133 mg, 0.35 mmol) in DMF (3 mL) was stirred at room temperature for 4 hr. The mixture was concentrated, the residue was dissolved in ethyl acetate (15 mL), was washed with 0.5 N HCl (1 x 5 mL), sat. $NaHCO_3$ (1x 5 mL), brine (1 x 5 mL) and was dried ($MgSO_4$). The residue obtained upon evaporation was chromatographed on 25 g of silica gel, eluting with 3:1 ethyl acetate:hexane to give N-[(2-chloro-6-methylphenyl)carbonyl]-4-(5-chloro-1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester (54 mg). LR(+)LSIMS : m/z 962 (2M+NH4), 945 (2M+H), 490 (M+NH4), 473 (M+H (2 Cl)).

Example 8.

N-[(2-chloro-6-methylphenyl)carbonyl]-4-(5-chloro-1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine.

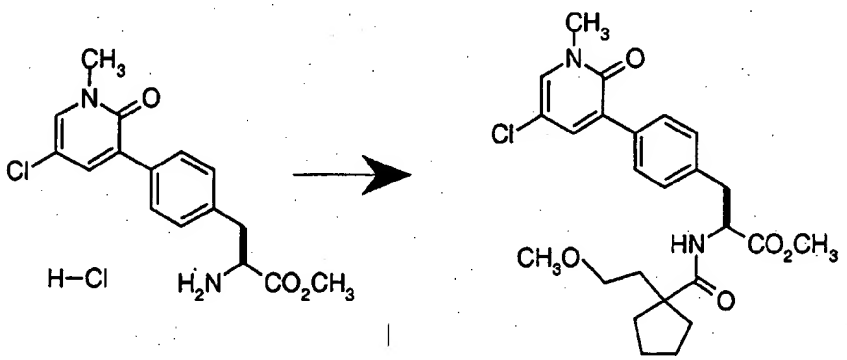


A solution of N-[(2-chloro-6-methylphenyl)carbonyl]-4-(5-chloro-1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester (51 mg, 0.108 mmol) in THF (3

mL) was treated with a solution of lithium hydroxide monohydrate (18 mg, 0.43 mmol) in water (1.0 mL). Additional THF was added to effect a clear solution and the reaction mixture was stirred 1 hr. TLC (ethyl acetate) indicated starting material was consumed. A few drops of acetic were added and the entire reaction mixture was applied to a 4 x 30 cm, C-18 reversed phase HPLC column and eluted with a linear gradient of acetonitrile in water of 5 to 95% over 35 min. The product containing fraction was lyophillyzed to give N-[(2-chloro-6-methylphenyl)-carbonyl]-4-(5-chloro-1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine (40 mg, 82%) as a white solid. LR-Electrospray : m/z positive ion, 481(M+Na), 459(M+H (2 Cl)); negative ion, 457 (M-H (2 Cl)).

Example 9.

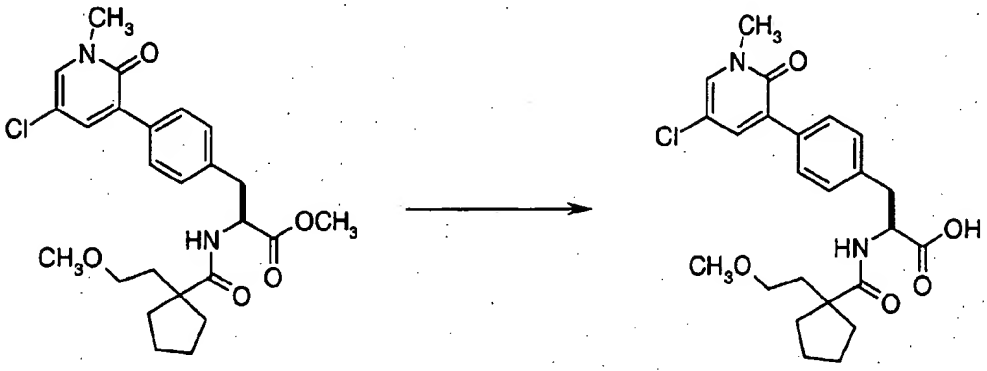
4-(5-chloro-1-methyl-2-oxo-3-pyridinyl)-N-[[1-(2-methoxyethyl)cyclopentyl]-carbonyl]-L-phenylalanine methyl ester



A solution of 4-(5-chloro-1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester hydrochloride (47.4 mg, 0.25 mmol), 1-(2-methoxyethyl)cyclopentane carboxylic acid (47 mg, 0.28 mmol), DIEA (175 µL, 1.0 mmol) and HBTU (133 mg, 0.35 mmol) in DMF (3 mL) was stirred at room temperature for 4 hr. The mixture was concentrated, the residue was dissolved in ethyl acetate (15 mL), was washed with 0.5 N HCl (1 x 5 mL), sat. $NaHCO_3$ (1 x 5 mL), brine (1 x 5 mL) and was dried ($MgSO_4$). The residue obtained upon evaporation was chromatographed on 25 g of silica gel, eluting with ethyl acetate to give 4-(5-chloro-1-methyl-2-oxo-3-pyridinyl)-N-[[1-(2-methoxyethyl)cyclopentyl]carbonyl]-L-phenylalanine methyl ester (70.5 mg, 59%). LR-Electrospray : m/z positive ion, 943 (2M+Na), 483 (M+Na), 478, (M+NH4), 461 (M+H); negative ion 919 (2M-H), 521, 459 (M-H).

Example 10.

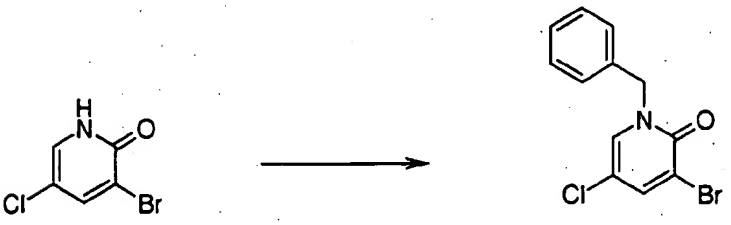
4-(5-chloro-1-methyl-2-oxo-3-pyridinyl)-N-[[1-(2-methoxyethyl)cyclopentyl]-carbonyl]-L-phenylalanine



A solution of 4-(5-chloro-1-methyl-2-oxo-3-pyridinyl)-N-[[1-(2-methoxy-ethyl)cyclopentyl]carbonyl]-L-phenylalanine methyl ester (69 mg, 0.145 mmol) in THF (3 mL) was treated with a solution of lithium hydroxide monohydrate (24.3 mg, 0.58 mmol) in water (1.0 mL). Sufficient THF was added to the mixture to effect solution. The mixture was stirred 1 hr and a few drops of acetic acid were added. The entire reaction mixture was applied to a 4 x 30 cm, C-18 reversed phase HPLC column and eluted with a linear gradient of acetonitrile in water of 5 to 95% over 35 min. The product containing fraction was lyophillyzed to give 4-(5-chloro-1-methyl-2-oxo-3-pyridinyl)-N-[[1-(2-methoxyethyl)cyclopentyl]carbonyl]-L-phenylalanine (48 mg, 72%) as a white solid. LR-Electrospray: m/z positive ion 943 (2M+Na), 483 (M+Na), 478, (M+NH4), 461 (M+H); negative ion 919 (2M-H), 521, 459 (M-H).

Example 11.

1-Benzyl-3-bromo-5-chloro-2-pyridone

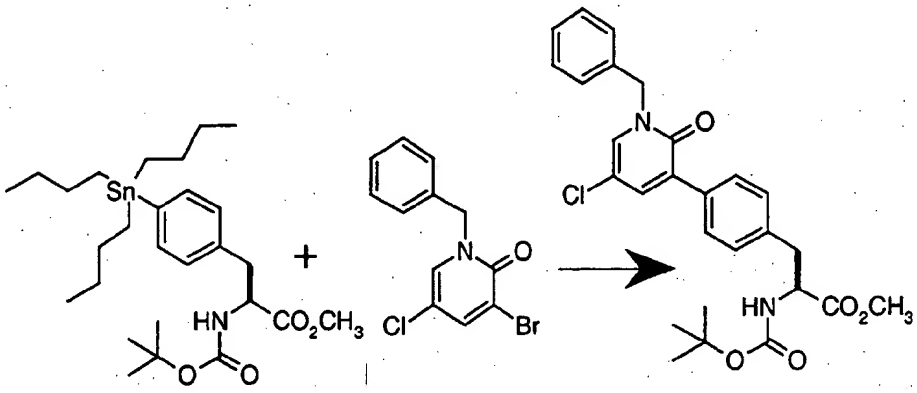


A mixture of 3-bromo-5-chloro-1H-2-pyridone (950 mg, 4.56 mmol), freshly ground potassium carbonate (1.26 g, 9.1 mmol) and tetrabutyl ammonium

chloride (100 mg) in was stirred mechanically without solvent for 30 min and benzyl bromide (0.56 mL, 4.7 mmol) was added. The mixture was stirred at room temperature for 72 hr. The mixture was diluted with ethyl acetate and filtered, washing the solids with ethyl acetate. The filtrate was evaporated to dryness and the residue was triturated with several portions of hexane. The residue was chromatographed over 90 g of silica gel eluting with 3:1 hexane:ethyl acetate followed by 100% ethyl acetate to give 1-benzyl-3-bromo-5-chloro-2-pyridone (423 mg, 31%), mp 108-110 °C. LR(+)LSIMS : m/z 595 (2M+H, 2 Cl,2 Br), 298 (M+H,1 Cl, 1 Br).

Example 12.

4-(1-Benzyl-5-chloro-2-oxo-3-pyridinyl)-N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanine methyl ester

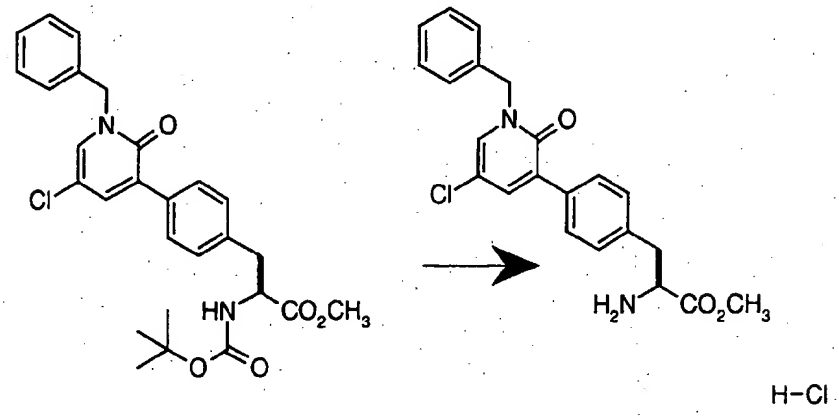


A solution of 1-benzyl-3-bromo-5-chloro-2-pyridone (296 mg, 0.98 mmol) and N-[(1,1-dimethylethoxy)carbonyl]-4-[(tributyl)stannyl]-L-phenylalanine methyl ester (560 mg, 0.99 mmol) in DMF (15 mL) was deoxygenated by alternately freezing the mixture in a liquid nitrogen bath under vacuum and thawing under argon (3 x). Bis(triphenylphosphine)palladium dichloride (80 mg, 0.11 mmol) was added and the mixture was heated to 90 °C for 4 hr as the mixture turned dark. An additional 60 mg of the catalyst was added and heating continued for 2 hr. The mixture was allowed to cool, was diluted with dichloromethane, and was filtered through a pad of celite. The filtrate was evaporated to dryness and the residue was chromatographed over 150 g of silica gel eluting with 1:2 ethyl acetate:hexane to give 4-(1-benzyl-5-chloro-2-oxo-3-pyridinyl)-N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanine methyl ester (255 mg, 52%). LMS-Electrospray: m/z 1015 (2M+Na) (4 Cl) 519 (M+Na) 514 (M+NH4)

497 (M+H).

Example 13.

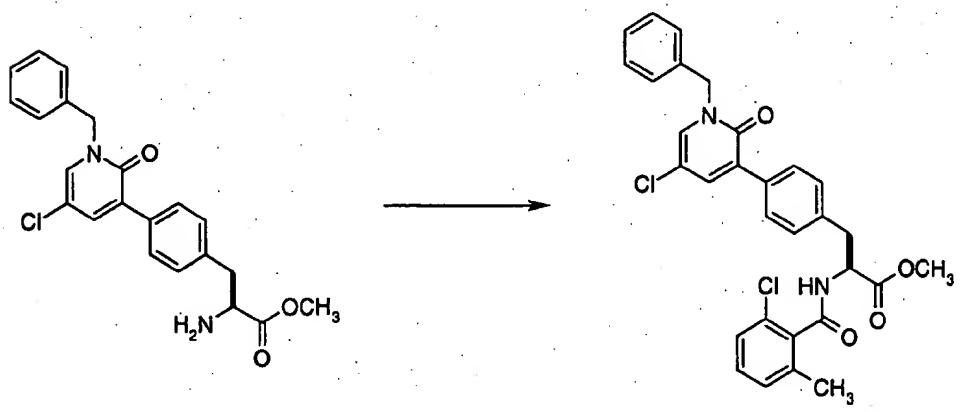
4-(1-Benzyl-5-chloro-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester hydrochloride



A solution of 1-benzyl-4-(5-chloro-2-oxo-3-pyridinyl)-N-[(1,1-dimethylethoxy)-carbonyl]-L-phenylalanine methyl ester (248 mg, 0.50 mmol) in 4 N HCl in dioxane (10 mL) was stirred for 1 hr and was concentrated. The residue was triturated with ether (15 mL) and was filtered to give 4-(1-benzyl-5-chloro-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester (202 mg, 94%) as a white powder. LR-Electrospray : m/z 1015 (2M+Na, 4 Cl), 519 (M+Na) 514 (M+NH4), 497 (M+H). HRMS: Obs. Mass 496.1774. Calcd. Mass 496.1765 (M+H).

Example 14.

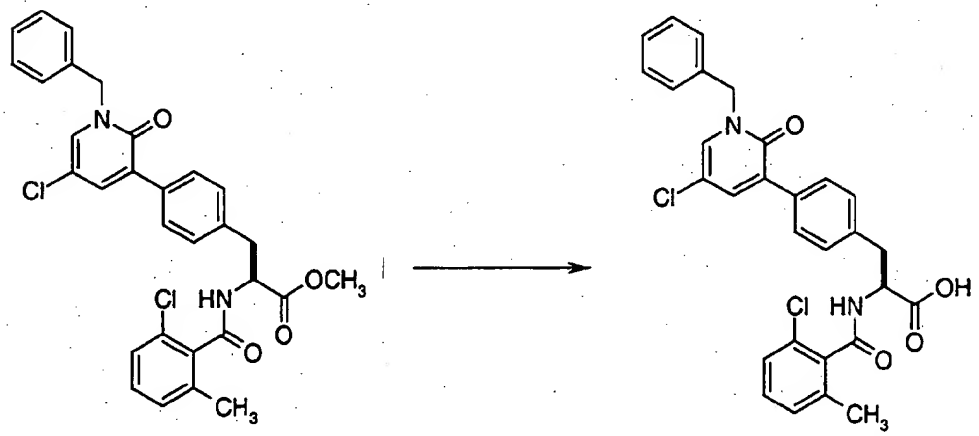
4-(1-Benzyl-5-chloro-2-oxo-3-pyridinyl)-N-[(2-chloro-6-methylphenyl)carbonyl]-L-phenylalanine methyl ester



A solution of 4-(1-benzyl-5-chloro-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester hydrochloride (100 mg, 0.23 mmol), 2-chloro-6-methylbenzoic acid (47 mg, 0.28 mmol), DIEA (200 µL, 1.2 mmol) and HBTU (133 mg, 0.35 mmol) in DMF (2 mL) was stirred at room temperature for 18 hr. The mixture was concentrated, the residue was dissolved in ethyl acetate (15 mL), was washed with 0.5 N HCl (1 x 5 mL), sat. $NaHCO_3$ (1 x 5 mL), brine (1 x 5 mL) and was dried ($MgSO_4$). The residue obtained upon evaporation was chromatographed on 25 g of silica gel, eluting with 45:55 ethyl acetate:hexane to give 4-(1-benzyl-5-chloro-2-oxo-3-pyridinyl)-N-[(2-chloro-6-methylphenyl)carbonyl]-L-phenylalanine methyl ester (74 mg, 58%). Obs. Mass 397.1313. Calcd. Mass 397.1320 (M+H)

Example 15.

4-(1-Benzyl-5-chloro-2-oxo-3-pyridinyl)-N-[(2-chloro-6-methylphenyl)carbonyl]-L-phenylalanine

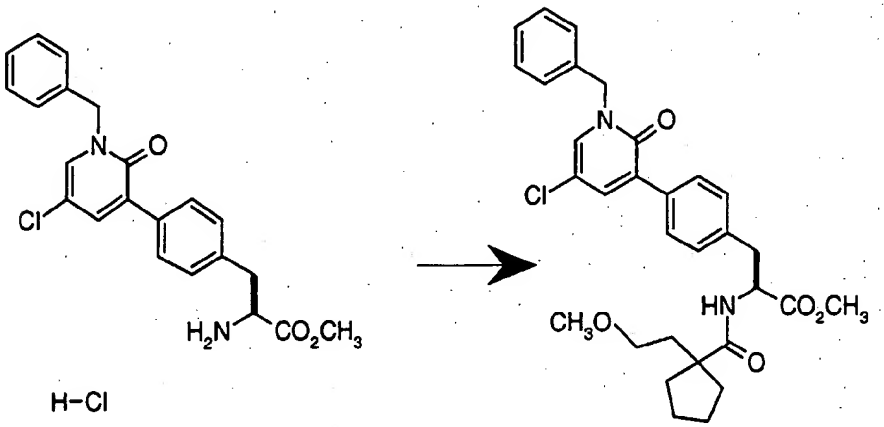


A solution of N-[(2-chloro-6-methylphenyl)carbonyl]-4-(1-benzyl-5-chloro-2-oxo-pyridinyl)-L-phenylalanine methyl ester (72 mg, 0.13 mmol) in THF (3 mL) was treated with a solution of lithium hydroxide monohydrate (22 mg, 0.52 mmol) in water (1.0 mL). Additional THF was added to effect a clear solution and the reaction mixture was stirred 1.5 hr at which time, TLC (ethyl acetate) indicated starting material was consumed. A few drops of acetic were added and the entire reaction mixture was applied to a 4 x 30 cm, C-18 reversed phase HPLC column and eluted with a linear gradient of acetonitrile in water of 5 to 95% over 35 min. The product containing fraction was lyophillyzed to give 4-(1-benzyl-5-chloro-2-oxo-3-pyridinyl)-N-[(2-chloro-6-methylphenyl)carbonyl]-L-phenylalanine (50 mg, 71%) as a white solid. LR-Electrospray : m/z negative ion 533 (M-H (2 Cl));

positive ion 557(M+Na), 552 (M+NH4), 535 (M+H (2 Cl)). HRMS: Obs. Mass 535.1190. Calcd. Mass 535.1191 (M+H).

Example 16.

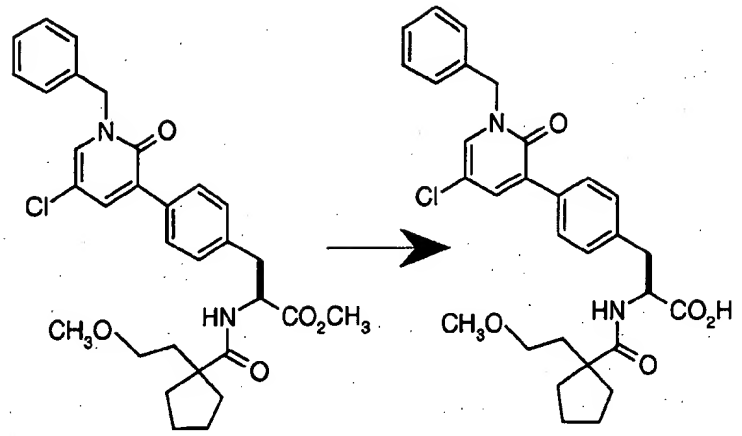
4-(1-Benzyl-5-chloro-2-oxo-3-pyridinyl)-N-[[1-(2-methoxyethyl)cyclopentyl]-carbonyl]-L-phenylalanine methyl ester.



A solution of 4-(1-benzyl-5-chloro-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester hydrochloride (100 mg, 0.25 mmol), 1-(2-methoxyethyl)cyclopentane carboxylic acid (47 mg, 0.28 mmol), DIEA (200 µL, 1.2 mmol) and HBTU (133 mg, 0.35 mmol) in DMF (2 mL) was stirred at room temperature for 18 hr. The mixture was concentrated, the residue was dissolved in ethyl acetate (15 mL), was washed with 0.5 N HCl (1 x 5 mL), sat. $NaHCO_3$ (1x 5 mL), brine (1 x 5 mL) and was dried ($MgSO_4$). The residue obtained upon evaporation was chromatographed on 25 g of silica gel, eluting with 60:40 ethyl acetate:hexane to give 4-(1-benzyl-5-chloro-2-oxo-3-pyridinyl)-N-[[1-(2-methoxyethyl)cyclopentyl]carbonyl]-L-phenylalanine methyl ester (80 mg, 63%). LR-Electrospray : m/z 1123 (2M+Na), 1118 (2M+NH4), 573 (M+Na),
568 (M+NH4), 551 (M+H (1 Cl)). HRMS: Obs. Mass 551.2297. Calcd. Mass 551.2313 (M+H).

Example 17.

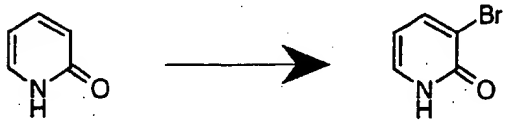
4-(1-Benzyl-5-chloro-2-oxo-3-pyridinyl)- N-[[1-(2-methoxyethyl)cyclopentyl]-carbonyl]-L-phenylalanine



A solution of 4-(1-benzyl-5-chloro-2-oxo-3-pyridinyl)-N-[[1-(2-methoxyethyl)cyclopentyl]carbonyl]-L-phenylalanine methyl ester (78 mg, 0.142 mmol) in THF (3 mL) was treated with a solution of lithium hydroxide monohydrate (24 mg, 0.57 mmol) in water (1.0 mL). Sufficient THF was added to the mixture to effect solution. The mixture was stirred 1 hr and a few drops of acetic acid were added. The entire reaction mixture was applied to a 4 x 30 cm, C-18 reversed phase HPLC column and eluted with a gradient of acetonitrile in water of 5- to 95% over 35 min. The product containing fraction was lyophillyzed to give 4-(5-chloro-1-benzyl-2-oxo-3-pyridinyl)- N-[[1-(2-methoxyethyl)cyclopentyl]-carbonyl]-L-phenylalanine (45 mg, 60%) as a white solid. LRMS-Electrospray: m/z positive ion 559 (M+Na), 554 (M+NH4), 537 (M+H (1 Cl)); negative ion 535 (M-H (1 Cl)). HRMS: obs. mass 537.2151. calcd. mass 537.2156 (M+H).

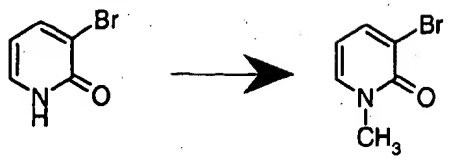
Example 18.

3-Bromo-1H-2-pyridone.



To a solution of 1H-2-pyridone (1.9 g, 20 mmol) in 1M aqueous potassium bromide (20 mL) was added a solution of bromine (3.2 g, 20 mmol) in 1 M aqueous potassium bromide (40 mL) over 5 min. The reaction was allowed to proceed overnight and the resulting precipitate was collected to give 1.4 g. Recrystallization from acetonitrile afforded 0.78 g of 3-bromo-1H-2-pyridone.

Example 19.

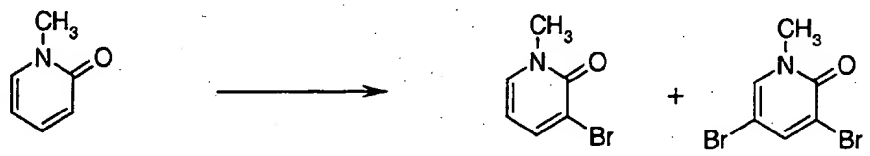


3-Bromo-1-methyl-2-pyridone.

A mixture of 3-bromo-1H-2-pyridone (740 mg, 4.25 mmol), potassium carbonate (1.18g, 8.5 mmol) and iodomethane (2.65 mL, 42.5 mmol) in DME (10 mL) was heated to reflux overnight. The mixture was filtered, washing with ethyl acetate and the filtrate was evaporated to dryness. The residue was purified by dry column chromatography over 27 g of silica gel, eluting with ethyl acetate to give 3-bromo-1-methyl-2-pyridone (0.63 g, 79%). LRMS (electrospray), positive ion, 188 (M+H).

Example 20.

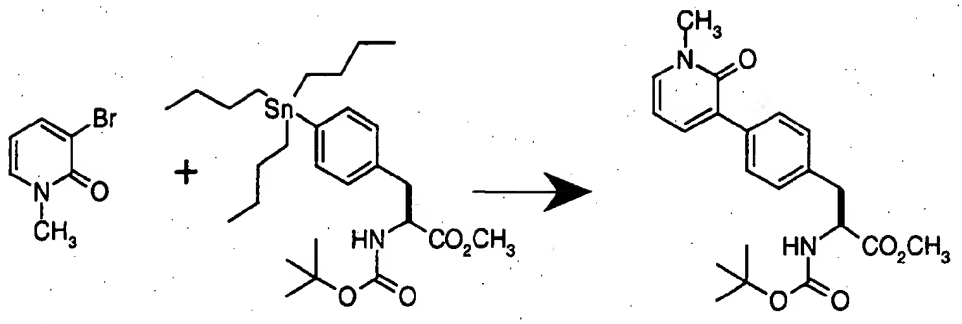
3-bromo-1-methyl-2-pyridone and 3,5-dibromo-1-methyl-2-pyridone



A solution of 1-methyl-2-pyridone (2.73 g, 25 mmol) and bromine (1.4 mL, 27 mmol) in glacial acetic acid (150 mL) was stirred 48 hr at room temperature. The mixture was concentrated. The residue was taken up in water (100 mL), made basic to litmus paper with 10 N sodium hydroxide and was extracted with dichloromethane (3 x 50 mL). The combined extracts were washed with brine (30 mL) and dried ($MgSO_4$). Filtration and evaporation of the solvent gave 4.7 g, which was purified by dry chromatography over 150 g of silica gel, eluting with 1:6 ethyl acetate:hexane followed by 1:1 ethyl acetate:hexane. The first compound to elute was 3,5-dibromo-1-methyl-2-pyridone (2.0 g, 30%), LR-Electrospray : m/z 266 (M+H (2 Br)). NMR(CDCl3) δ 3.597 (s, 3H), 7.426 (d, j = 2.7, 1H), 7.791 (d, j = 2.7, 1H). The second compound to elute was 3-bromo-1-methyl-2-pyridone (1.39 g, 30%), LR-Electrospray : m/z positive ion 251 (M+Na+CH3CN), 188 (M+H).

Example 21.

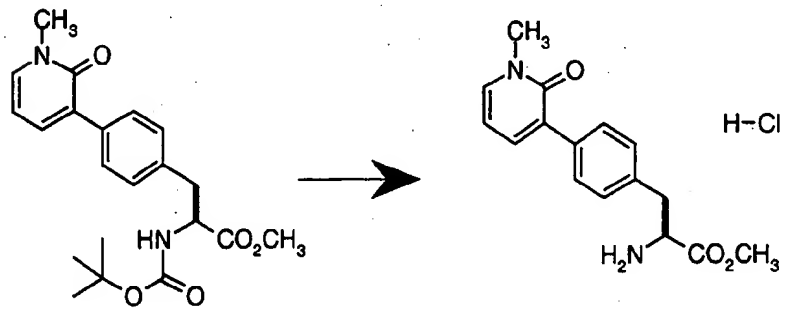
N-[(1,1-Dimethylethoxyl)carbonyl]-4-(1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester.



A solution of 3-bromo-1-methyl-2-pyridone (94 mg, 0.50 mmol) and N-[(1,1-dimethylethoxy)carbonyl]-4-[(tributyl)stannyl]-L-phenylalanine methyl ester (284 mg, 0.50 mmol) in DMF (3 mL) was deoxygenated by alternately freezing the mixture in a liquid nitrogen bath under vacuum and thawing under argon (3 X). bis(triphenylphosphine)palladium dichloride (40 mg, 0.057 mmol) was added and the mixture was heated to 90 °C for 3 hr as the mixture turned dark. TLC indicated that the reaction was not complete and an additional 20 mg portion of the catalyst was added and heating continued for 4 hr. The mixture was allowed to cool and was diluted with dichloromethane (20 mL) and was filtered through a pad of celite. The filtrate was evaporated to dryness and the residue was dissolved in 1:1 ether:ethyl acetate (20 mL). The solution was washed with water (1 x 10 mL), 5% potassium fluoride (2 x 5 mL) and water (1 x 10 mL) and was dried ($MgSO_4$). The residue obtained upon concentration was chromatographed over 25 g of silica gel eluting with 4:6 ethyl acetate:hexane to give N-[(1,1-dimethylethoxyl)carbonyl]-4-(1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester (64 mg, 33%). LRMS-Electrospray: m/z positive ion, 795 (2M+Na) 409 (M+Na) 387 (M+H). HRMS: Obs. Mass 387.1935. Calcd. Mass 387.1920 (M+H).

Example 22.

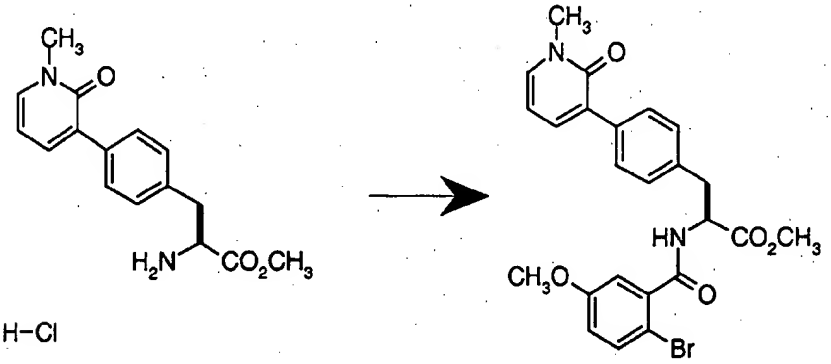
4-(1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester hydrochloride



A solution of N-[(1,1-dimethylethoxyl)carbonyl]-4-(1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester (60 mg, 0.155 mmol) in 4 N HCl in dioxane (4 mL) was stirred for 2 hr and was concentrated. The residue was triturated with several portions of ether to give 4-(1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester hydrochloride (55 mg, quant) as a white powder. LRMS-Electrospray : m/z positive ion 573 (2M+H) 328 (M+H+CH3CN) 319 (M+H+CH3OH) 287 (M+H). HRMS: Obs. Mass 287.1396. Calcd. Mass 287.1396 (M+H)

Example 23.

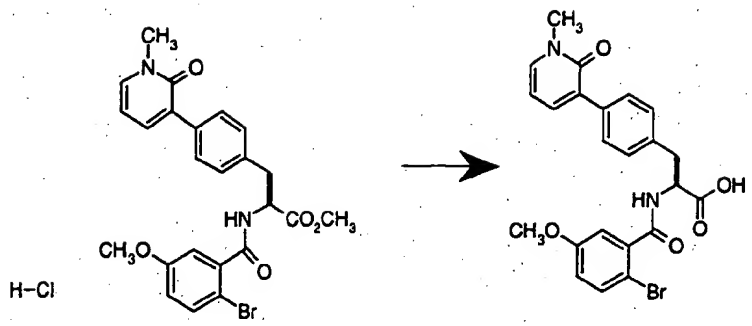
N-[(2-bromo-5-methoxyphenyl)carbonyl]-4-(1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester.



A solution of 4-(1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester hydrochloride (52 mg, 0.16 mmol), 2-bromo-5-methoxybenzoic acid (45 mg, 0.19 mmol), DIEA (140 µL, 0.80 mmol) and HBTU (85 mg, 0.22 mmol) in DMF (3 mL) was stirred at room temperature for 18 hr. The mixture was concentrated, the residue was dissolved in ethyl acetate (15 mL), was washed with 0.5 N HCl (1 x 5 mL), sat. $NaHCO_3$ (1x 5 mL), brine (1 x 5 mL) and was dried ($MgSO_4$). The residue obtained upon evaporation (85 mg) was chromatographed on 25 g of silica gel, eluting with ethyl acetate to give N-[(2-bromo-5-methoxyphenyl)carbonyl]-4-(1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester (54 mg, 68%). HRMS: Obs. Mass 499.0872. Calcd. Mass 499.0869 (M+H)

Example 24.

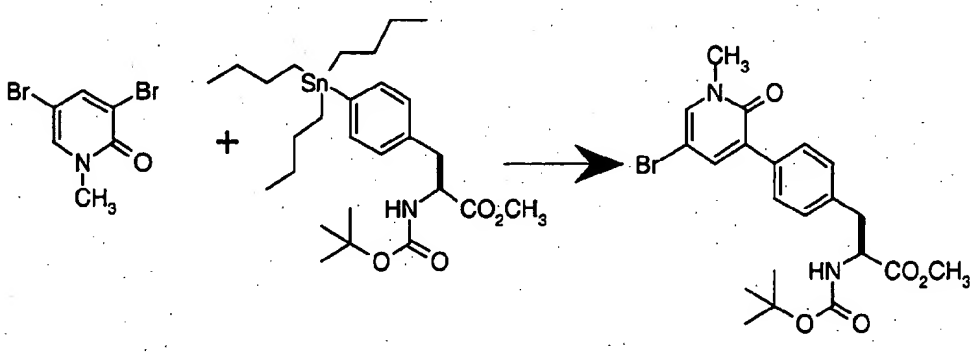
N-[(2-bromo-5-methoxyphenyl)carbonyl]-4-(1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine



A solution of N-[(2-bromo-5-methoxyphenyl)carbonyl]-4-(1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester (52 mg, 0.104 mmol) in THF (3 mL) was treated with a solution of lithium hydroxide monohydrate (20 mg, 0.47 mmol) in water (1.0 mL). Methanol (0.5 mL) was added to effect a clear solution and the reaction mixture was stirred 18 hr. Acetic acid (0.5 mL) was added, the entire reaction mixture was applied to a 4 x 30 cm, C-18 reversed phase HPLC column and eluted with a gradient of acetonitrile in water of 5 to 95% over 35 min. The product containing fraction was lyophillyzed to give N-[(2-bromo-5-methoxyphenyl)carbonyl]-4-(1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine (39 mg, 78%) as a white solid. HRMS: Obs. Mass 485.0703 Calcd. Mass 485.0712 (M+H).

Example 25.

4-(5-bromo-1-methyl-2-oxo-3-pyridinyl)-N-[(1,1-dimethylethoxyl)carbonyl]-L-phenylalanine methyl ester.

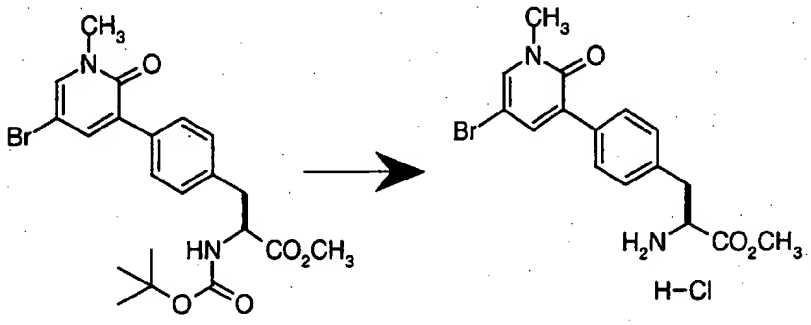


A solution of 3,5-dibromo-1-methyl-2-pyridone (267 mg, 1.0 mmol) and N-[(1,1-dimethylethoxy)carbonyl]-4-[(tributyl)stannyl]-L-phenylalanine methyl ester (568 mg, 1.0 mmol) in DMF (7 mL) was deoxygenated by alternately freezing the mixture in a liquid nitrogen bath under vacuum and thawing under argon (3 X). bis(triphenylphosphine)palladium dichloride (80 mg, 0.11 mmol) was added and

the mixture was heated to 90 °C for 3 hr as the mixture turned dark. TLC indicated that the reaction was not complete and an additional 40 mg portion of the catalyst was added and heating continued for 4 hr. The mixture was allowed to cool and was diluted with dichloromethane (40 mL) and was filtered through a pad of celite. The filtrate was evaporated to dryness and the residue was dissolved in ethyl acetate (30 mL). The solution was washed with water (1 x 10 mL), 5% potassium fluoride (2 x 10 mL) and brine (1 x 5 mL) and was dried ($MgSO_4$). The residue obtained upon concentration was chromatographed over 45 g of silica gel eluting with 3:7 ethyl acetate:hexane to give 4-(5-bromo-1-methyl-2-oxo-3-pyridinyl)-N-[(1,1-dimethylethoxyl)carbonyl]-L-phenylalanine methyl ester (140 mg, 30%). FAB MS: 465 (M+H (1 Br)).

Example 26.

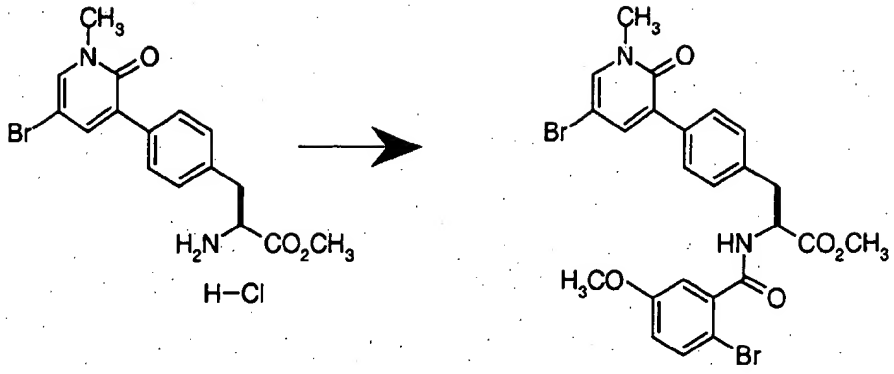
4-(5-bromo-1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester hydrochloride



A solution of N-[(1,1-dimethylethoxyl)carbonyl]-4-(5-bromo-1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester (135 mg, 0.29 mmol) in 4 N HCl in dioxane (5 mL) was stirred for 2 hr and was concentrated. The residue was triturated with several portions of ether to give 4-(5-bromo-1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester hydrochloride (120 mg, quant) as a white powder. LRMS-Electrospray : m/z positive ion 729, 2M+H (2 Br), 406 (M+H+CH3CN), 397 (M+H+CH3CN (1 Br)), 365 (M+H (1 Br)). HRMS: Obs. Mass 365.0504. Calcd. Mass 365.0501 (M+H).

Example 27.

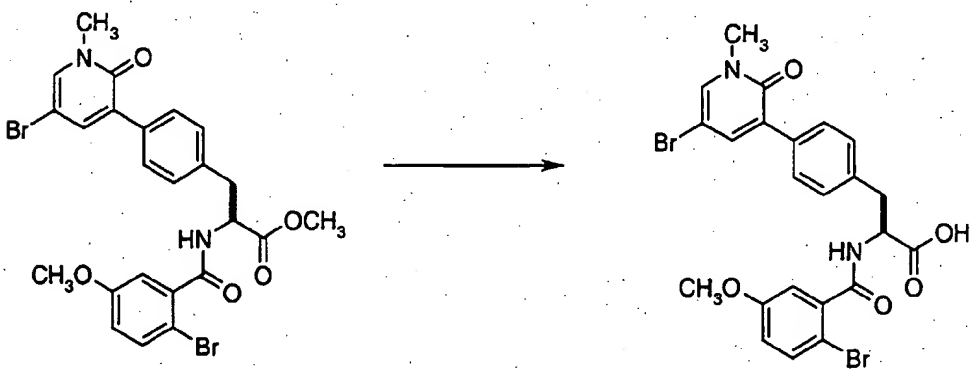
N-[(2-bromo-5-methoxyphenyl)carbonyl]-4-(5-bromo-1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester



A solution of 4-(5-bromo-1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester hydrochloride (120 mg, 0.30 mmol), 2-bromo-5-methoxybenzoic acid (82 mg, 0.36 mmol), DIEA (260 µL, 1.5 mmol) and HBTU (157 mg, 0.41 mmol) in DMF (4 mL) was stirred at room temperature for 18 hr. The mixture was concentrated, the residue was dissolved in ethyl acetate (15 mL), was washed with 0.5 N HCl (1 x 5 mL), sat. $NaHCO_3$ (1x 5 mL), brine (1 x 5 mL) and was dried ($MgSO_4$). The residue obtained upon evaporation (180 mg) was chromatographed on 25 g of silica gel, eluting with 3:1 ethyl acetate:hexane to give N-[(2-bromo-5-methoxyphenyl)carbonyl]-4-(5-bromo-1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester (130 mg, 76%). HRMS: Obs. Mass 576.9959. Calcd. Mass 576.9973 (M+H)

Example 28.

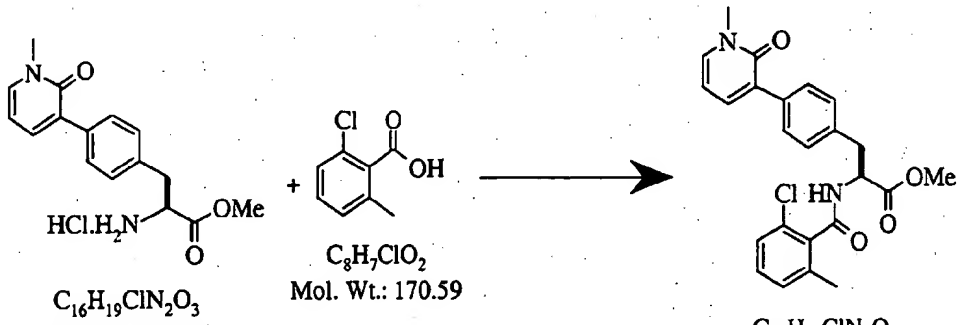
N-[(2-bromo-5-methoxyphenyl)carbonyl]-4-(5-bromo-1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine



A solution of N-[(2-bromo-5-methoxyphenyl)carbonyl]-4-(5-bromo-1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester (29 mg, 0.05 mmol) in THF (3 mL) was treated with a solution of lithium hydroxide monohydrate (20 mg, 0.47 mmol)

in water (1.0 mL). Methanol (0.5 mL) was added to effect a clear solution and the reaction mixture was stirred 18 hr. Acetic acid (0.5 mL) was added, the entire reaction mixture was applied to a 4 x 30 cm, C-18 reversed phase HPLC column and eluted with a gradient of acetonitrile in water of 5 to 95% over 35 min. The product containing fraction was lyophillyzed to give N-[(2-bromo-5-methoxyphenyl)carbonyl]-4-(5-bromo-1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine (22 mg, 79%) as a white solid. HRMS: Obs. Mass 562.9814. Calcd. Mass 562.9817 (M+H).

Example 29. Preparation of N-[(2-chloro-6-methylphenyl)carbonyl]-4-(1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester



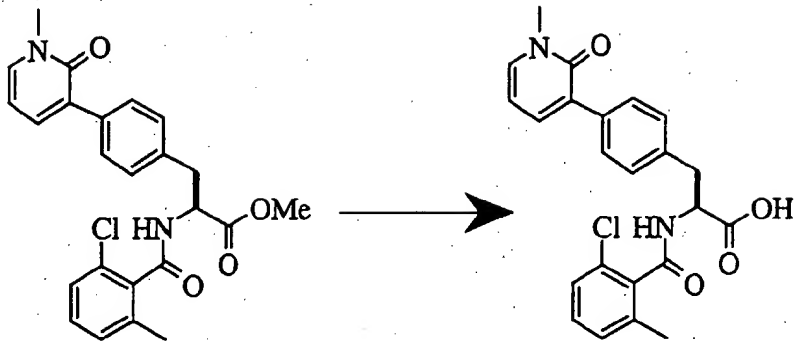
$C_{16}H_{19}ClN_2O_3$
Mol. Wt.: 322.79

$C_8H_7ClO_2$
Mol. Wt.: 170.59

$C_{24}H_{23}ClN_2O_4$
Mol. Wt.: 438.90

To a suspension of 4-(1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester hydrochloride salt (101 mg, 0.313 mmol), 2-chloro-6-methylbenzoic acid (60 mg, 0.35 mmol) and HBTU (133 mg, 0.35 mmol) in DMF (2 mL) was added DIEA (122 μL, 0.88 mmol) at room temperature. The resulting mixture was stirred for 15 h. Then, the mixture was poured into water (25 mL) and the organic compound was extracted into ethyl acetate (2 x 15 mL). The combined ethyl acetate extracts were washed successively with 0.5 N HCl (25 mL), saturated $NaHCO_3$ solution (25 mL), brine solution (25 mL) and were dried over anhydrous magnesium sulfate. Filtration of the drying agent and concentration gave the crude product which was purified by silica gel chromatography using a Biotage (40s) column to afford 122 mg (88% yield) of N-[(2-chloro-6-methylphenyl)carbonyl]-4-(1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester as an amorphous white solid. FAB-HRMS m/e calcd for $C_{24}H_{23}ClN_2O_4$ (M+H) 439.1425, found 439.1414.

Example 30. Preparation of N-[(2-chloro-6-methylphenyl)carbonyl]-4-(1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine



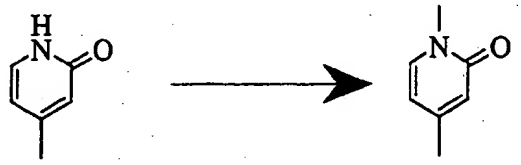
$C_{24}H_{23}ClN_2O_4$
Mol. Wt.: 438.90

$C_{23}H_{21}ClN_2O_4$
Mol. Wt.: 424.88

To a suspension of N-[(2-chloro-6-methylphenyl)carbonyl]-4-(1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester (118 mg, 0.269 mmol) in ethanol (6 mL) was added 1N aqueous sodium hydroxide solution (4 mL) at room temperature. The resulting solution was heated to 50 °C and stirred for 2 h. Then, the ethanol was removed under vacuum and the residue was diluted with water (25 mL). The aqueous solution was washed with diethyl ether (25 mL) to remove any neutral impurities. The aqueous layer was acidified with 1.0 N HCl and the product was extracted into ethyl acetate (2 x 25 mL). The combined organic extracts were washed with brine solution (50 mL) and were dried over anhydrous magnesium sulfate. Filtration of the drying agent and concentration afforded 81 mg (71% yield) of N-[(2-chloro-6-methylphenyl)carbonyl]-4-(1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine as a white solid: mp 204-210 °C. FAB-HRMS m/e calcd for $C_{23}H_{21}ClN_2O_4$ (M+H) 425.1268, found 425.1267.

Example 31. Preparation of N-[(2,6-dichlorophenyl)carbonyl]-4-(1,4-dimethyl-2-oxo-3-pyridinyl)-L-phenylalanine

a) Preparation of 1,4-dimethyl-2(1H)-pyridone



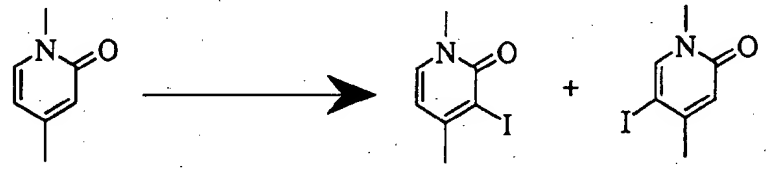
C_6H_7NO
Mol. Wt.: 109.13

C_7H_9NO
Mol. Wt.: 123.15

To a suspension of 4-methy-2(1H)-pyridone (5 g, 45.82 mmol) and potassium carbonate (12.64 g, 91.64 mmol) in DME (100 mL) was added iodomethane (50.5

g, 366 mmol) at room temperature and the reaction mixture was heated to reflux overnight. The reaction mixture was cooled to room temperature, poured into water (200 mL) and was extracted with ethyl acetate (3 x 100 mL). The combined extracts were washed with brine solution (200 mL) and were dried over anhydrous magnesium sulfate. Filtration of the drying agent and concentration gave the crude product which was purified by silica gel chromatography on a Biotage (40m) column to afford 2.5 g (44% yield) of 1,4-dimethyl-2(1H)-pyridone as an amorphous white solid. FAB-HRMS m/e calcd for C_7H_9NO (M+H) 123.0241, found 123.0246.

b) Preparation of 1,4-dimethyl-3-iodo-2(1H)-pyridone and 1,4-dimethyl-5-iodo-2(1H)-pyridone



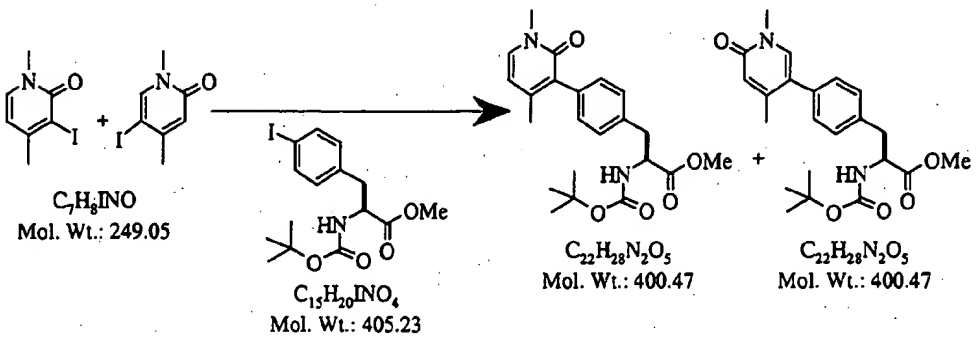
C_7H_9NO
Mol. Wt.: 123.15

C_7H_8INO
Mol. Wt.: 249.05

C_7H_8INO
Mol. Wt.: 249.05

A reaction mixture containing 1,4-dimethyl-2-pyridone (2.46 g, 20 mmol), trifluoroacetic acid (31 mL) and trifluoroacetic anhydride (6.25 mL) was refluxed for 5 min. Then, NIS (5.62 g, 25 mmol) was added and the mixture was stirred for 15 h. The reaction mixture was cooled to room temperature and the solvent was removed under vacuum. The residue was diluted with ethyl acetate (100 mL) and the white solid that formed was collected by filtration. The filtrate was washed with saturated sodium bicarbonate solution (2 x 100 mL), brine solution (100 mL) and was dried over anhydrous magnesium sulfate. Filtration of the drying agent and concentration of the solvent gave a crude product which was purified by silica gel chromatography on a Biotage (40m) column to afford 0.92 g (5% yield) of a ~1:1 mixture of 1,4-dimethyl-3-iodo-2(1H)-pyridone and 1,4-dimethyl-5-iodo-2(1H)-pyridone which was used directly in the next step. ^1H NMR (300 MHz, D6-DMSO, ppm) 8.06 (s, 1H), 7.6 (d, 1H, J = 5.5 Hz), 6.4 (s, 1H), 6.2 (d, 1H, J = 5.5 Hz), 3.4 (s, 3H), 3.3 (s, 3H), 2.3 (s, 3H), 2.15 (s, 3H).

c) Preparation of N-[(1,1-dimethylethoxyl)carbonyl]-4-(1,4-dimethyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester and N-[(1,1-dimethylethoxyl)carbonyl]-4-(1,4-dimethyl-2-oxo-5-pyridinyl)-L-phenylalanine methyl ester

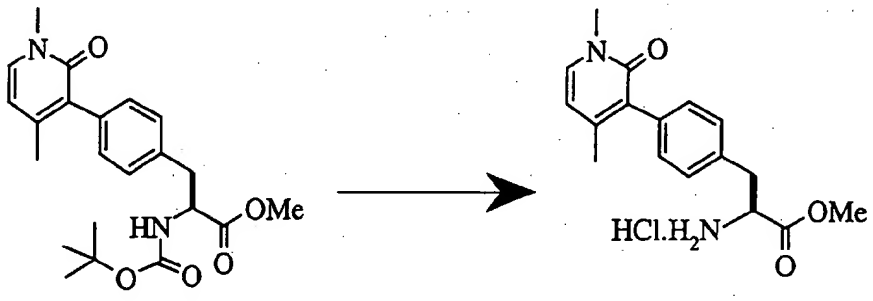


To a suspension of zinc dust (0.66 g, 10 mmol) in THF (1.0 mL) was added 1,2-dibromoethane (86 µL, 1 mmol)) at room temperature. This suspension was heated to 60-65 °C with a heat gun until evolution of ethylene gas ceased. Then, the suspension was cooled to room temperature and trimethylchlorosilane (0.126 mL, 1 mmol)) was added and the mixture was stirred for 15 min. A mixture of 1,4-dimethyl-3-iodo-2(1H)-pyridone and 1,4-dimethyl-5-iodo-2(1H)-pyridone (0.92 g, 3.69 mmol) in DMA (3 mL) was warmed to effect dissolution and was added in one portion to the reaction mixture. After addition, the mixture was heated to 70 °C and was stirred for 15 h, at which time the TLC analysis of an aliquot, which had been quenched with saturated ammonium chloride solution, indicated the absence of starting material. The reaction mixture was diluted with THF (4 mL) and was cooled to room temperature. The excess zinc dust was allowed to settle until a clear supernatant liquid formed (~3 h).

The above prepared solution containing the zinc compound (3.69 mmol) was added to a solution of $Pd(dba)_2$ (54 mg, 0.1 mmol), trifurylphosphine (102 mg, 0.4 mmol) and N-[(1,1-dimethylethoxy)carbonyl]-4-iodo-L-phenylalanine methyl ester (1.01 g, 2.5 mmol) in THF (4 mL) at room temperature and the light yellow mixture was stirred for 15 h at 50 °C. Then, the mixture was poured into a saturated ammonium chloride solution and was extracted with ethyl acetate (3 x 50 mL). The combined extracts were washed with brine solution (150 mL) and were dried over anhydrous magnesium sulfate. Filtration of the drying agent and concentration gave the crude product which was purified by silica gel chromatography on a Biotage (40m) column to obtain 0.141 g (14% yield) of N-[(1,1-dimethylethoxyl)carbonyl]-4-(1,4-dimethyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester as an amorphous white solid. ES-HRMS m/e calcd for $C_{22}H_{28}N_2O_5$

(M+Na) 423.1890, found 423.1894 and 0.350 g (35% yield) of N-[(1,1-dimethylethoxyl)carbonyl]-4-(1,4-dimethyl-2-oxo-5-pyridinyl)-L-phenylalanine methyl ester as an amorphous white solid. ES-HRMS m/e calcd for $C_{22}H_{28}N_2O_5$ (M+Na) 423.1890, found 423.1897.

d) Preparation of 4-(1,4-dimethyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester hydrochloride salt

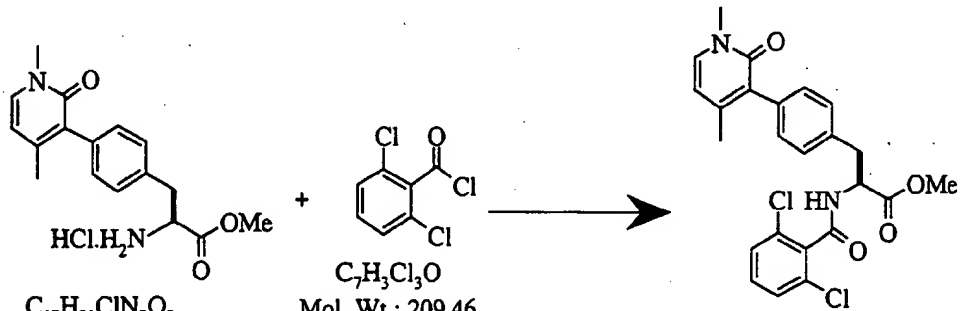


$C_{22}H_{28}N_2O_5$
Mol. Wt.: 400.47

$C_{17}H_{21}ClN_2O_3$
Mol. Wt.: 336.79

To a solution of N-[(1,1-dimethylethoxyl)carbonyl]-4-(1,4-dimethyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester (132 mg, 0.33 mmol) in dioxane (1 mL) was added 4 N HCl solution in dioxane (1.5 mL) at room temperature. The solution was stirred for 4 h and concentrated under vacuum. The residue was dissolved in methanol (5 ml) and toluene (5 mL) and concentrated under vacuum to give 111 mg (99% yield) of 4-(1,4-dimethyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester hydrochloride salt as an amorphous white solid. EI-HRMS m/e calcd for $C_{17}H_{20}N_2O_3$ (M^+) 300.1474, found 300.1486.

e) Preparation of N-[(2,6-dichlorophenyl)carbonyl]-4-(1,4-dimethyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester



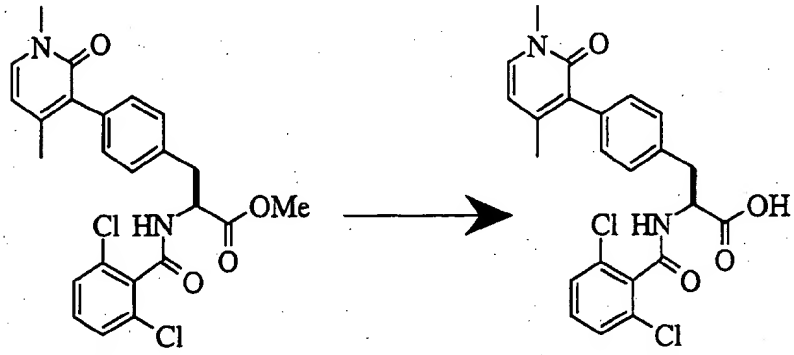
$C_{17}H_{21}ClN_2O_3$
Mol. Wt.: 336.85

$C_7H_3Cl_3O$
Mol. Wt.: 209.46

$C_{24}H_{22}Cl_2N_2O_4$
Mol. Wt.: 473.35

To a suspension of 4-(1,4-dimethyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester hydrochloride salt (34 mg, 0.1 mmol) and 2,6-dichlorobenzoyl chloride (25 mg, 0.12 mmol) in dichloromethane (2 mL) was added DIEA (174 µL, 1.0 mmol) at room temperature. After 5 min, a clear solution was obtained which was stirred for 72 h. Then, the mixture was concentrated, the residue was dissolved in ethyl acetate (25 mL), was washed with 0.5 N HCl (25 mL), saturated $NaHCO_3$ solution (25 mL), brine solution (15 mL) and was dried over anhydrous magnesium sulfate. Filtration of the drying agent and concentration gave crude product, which was purified by silica gel chromatography using a Biotage (40s) column, to afford 23 mg (49% yield) of N-[(2,6-dichlorophenyl)carbonyl]-4-(1,4-dimethyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester as an amorphous white solid. ES-HRMS m/e calcd for $C_{24}H_{22}Cl_2N_2O_4$ (M+Na) 495.0850, found 495.0859.

f) Preparation of N-[(2,6-dichlorophenyl)carbonyl]-4-(1,4-dimethyl-2-oxo-3-pyridinyl)-L-phenylalanine



$C_{24}H_{22}Cl_2N_2O_4$
Mol. Wt.: 473.35

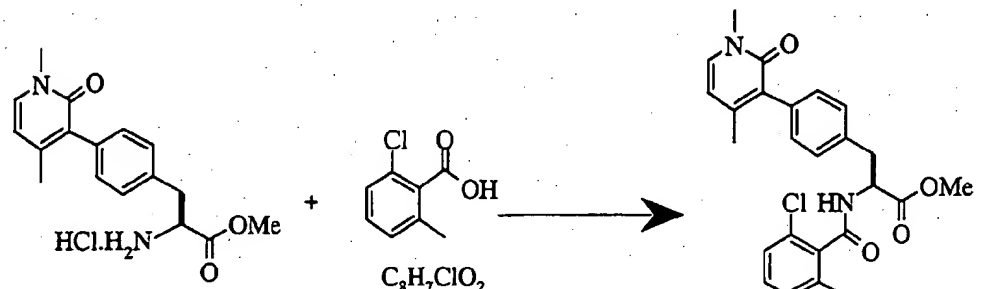
$C_{23}H_{20}Cl_2N_2O_4$
Mol. Wt.: 459.32

To a suspension of N-[(2,6-dichlorophenyl)carbonyl]-4-(1,4-dimethyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester (20 mg, 0.04 mmol) in ethanol (1 mL) was added 1N aqueous sodium hydroxide solution (0.5 mL) at room temperature. The mixture was heated to 40-45 °C and stirred for 3 h. Then, the ethanol was removed under vacuum and the residue was diluted with water (10 mL). The aqueous solution was washed with diethyl ether (25 mL) to remove any neutral impurities. The aqueous layer was acidified with 1.0 N HCl and the product was extracted into ethyl acetate (2 x 25 mL). The combined organic extracts were washed with brine solution (50 mL) and were dried over anhydrous magnesium sulfate. Filtration of the drying agent and concentration afforded 17 mg (89% yield) of N-[(2,6-dichlorophenyl)carbonyl]-4-(1,4-dimethyl-2-oxo-3-pyridinyl)-L-phenylalanine as

an amorphous white solid. ES-HRMS m/e calcd for $C_{23}H_{20}Cl_2N_2O_4$ (M+Na) 481.0691, found 481.0699.

Example 32. Preparation of N-[(2-chloro-6-methylphenyl)carbonyl]-4-(1,4-dimethyl-2-oxo-3-pyridinyl)-L-phenylalanine

a) Preparation of N-[(2-chloro-6-methylphenyl)carbonyl]-4-(1,4-dimethyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester



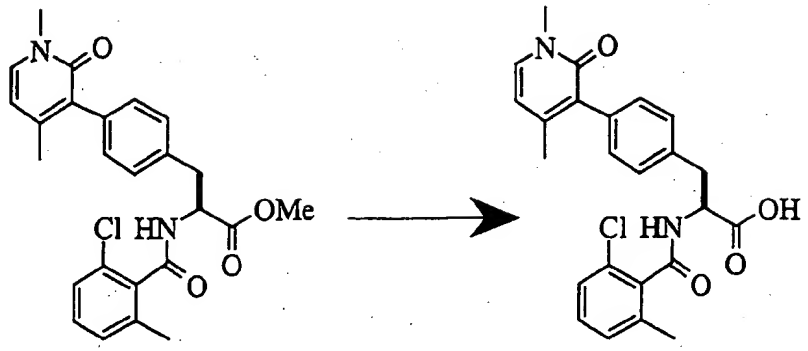
$C_{17}H_{21}ClN_2O_3$
Mol. Wt.: 336.85

$C_8H_7ClO_2$
Mol. Wt.: 170.59

$C_{25}H_{25}ClN_2O_4$
Mol. Wt.: 452.93

To a suspension of 4-(1,4-dimethyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester hydrochloride salt (68 mg, 0.2 mmol), 2-chloro-6-methylbenzoic acid (45 mg, 0.25 mmol) and HBTU (95 mg, 0.25 mmol) in DMF (1.5 mL) was added DIEA (174 μL, 1.0 mmol) at room temperature. The resulting solution was stirred for 72 h, the mixture was poured into water (25 mL) and was extracted with ethyl acetate (2 x 15 mL). The combined ethyl acetate extracts were washed successively with 0.5 N HCl (25 mL), saturated $NaHCO_3$ solution (25 mL), brine solution (25 mL) and were dried over anhydrous magnesium sulfate. Filtration of the drying agent and concentration of the solvent gave the crude product, which was purified by silica gel chromatography using a Biotage (40s) column to afford 24 mg (27% yield) of N-[(2-chloro-6-methylphenyl)carbonyl]-4-(1,4-dimethyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester as an amorphous white solid. ES-HRMS m/e calcd for $C_{25}H_{25}ClN_2O_4$ (M+Na) 475.1395, found 475.1400.

b) Preparation of N-[(2-chloro-6-methylphenyl)carbonyl]-4-(1,4-dimethyl-2-oxo-3-pyridinyl)-L-phenylalanine



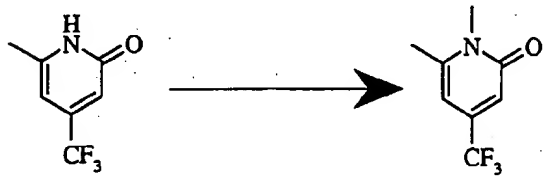
$C_{25}H_{25}ClN_2O_4$
Mol. Wt.: 452.93

$C_{24}H_{23}ClN_2O_4$
Mol. Wt.: 438.90

To a suspension of N-[(2-chloro-6-methylphenyl)carbonyl]-4-(1,4-dimethyl-2-oxo-3-pyridinyl)-L-phenylalanine methyl ester (22 mg, 0.048 mmol) in ethanol (1 mL) was added 1N aqueous sodium hydroxide solution (0.5 mL) at room temperature. The resulting solution was heated to 40-45 °C and stirred for 2 h. Then, the ethanol was removed under vacuum and the residue was diluted with water (25 mL). The aqueous solution was washed with diethyl ether (25 mL) to remove any neutral impurities. The aqueous layer was acidified with 1.0 N HCl and the product was extracted into ethyl acetate (2 x 25 mL). The combined extracts were washed with brine solution (50 mL) and were dried over anhydrous magnesium sulfate. Filtration of the drying agent and concentration afforded 18 mg (86% yield) of N-[(2-chloro-6-methylphenyl)carbonyl]-4-(1,4-dimethyl-2-oxo-3-pyridinyl)-L-phenylalanine as an amorphous white solid. ES-HRMS m/e calcd for $C_{24}H_{23}ClN_2O_4$ (M+H) 439.1419, found 439.1425.

Example 33. Preparation of N-[(2,6-dichlorophenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine

a) Preparation of 1,6-dimethyl-4-(trifluoromethyl)-2-pyridone

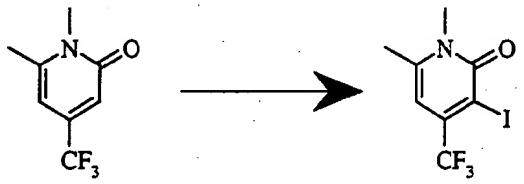


$C_7H_6F_3NO$
Mol. Wt.: 177.12

$C_8H_8F_3NO$
Mol. Wt.: 191.15

To a suspension of 6-methyl-4-(trifluoromethyl)-1H-2-pyridone (2 g, 11.25 mmol) and potassium carbonate (4.68 g, 33.9 mmol) in DME (25 mL) was added iodomethane (9.62 g, 67.8 mmol) at room temperature and the reaction mixture was heated to reflux overnight. The reaction mixture was cooled to room temperature, poured into water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The combined extracts were washed with brine solution (200 mL) and were dried over anhydrous magnesium sulfate. Filtration of the drying agent and concentration of the solvent gave the crude product which was purified by silica gel chromatography on a Biotage (40m) column to obtain 2.1 g (97% yield) of 1,6-dimethyl-4-(trifluoromethyl)-2-pyridone as a white solid: mp 80-82°C. EI-HRMS m/e calcd for $C_8H_8F_3NO$ (M^+) 191.0558, found 191.0559.

b) Preparation of 1,6-dimethyl-3-iodo-4-(trifluoromethyl)-2-pyridone

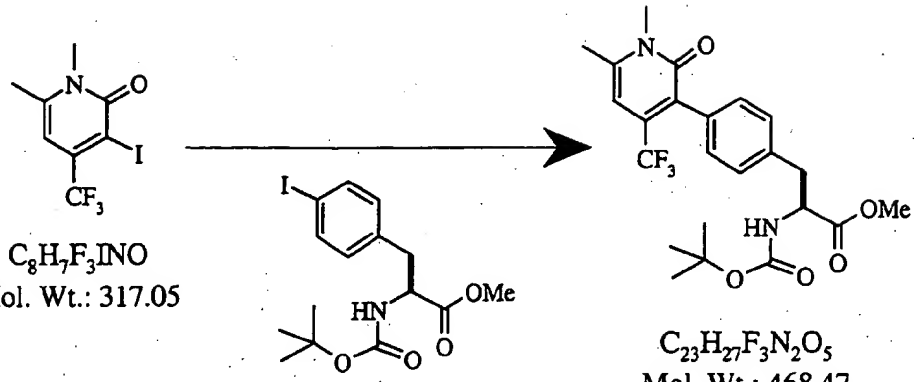


$C_8H_8F_3NO$ $C_8H_7F_3INO$

Mol. Wt.: 191.15 Mol. Wt.: 317.05

A mixture containing 1,6-dimethyl-4-(trifluoromethyl)-2-pyridone (2.1 g, 10.98 mmol), trifluoroacetic acid (18 mL) and trifluoroacetic anhydride (3.5 mL) was refluxed for 5 min. Then, NIS (3.15 g, 14 mmol) was added and the reaction mixture was stirred for 15 h. The reaction mixture was cooled to room temperature and the solvent was removed under vacuum. The residue was diluted with ethyl acetate (100 mL), was washed with saturated sodium bicarbonate solution (2 x 100 mL) and brine solution (100 mL) and was dried over anhydrous magnesium sulfate. Filtration of the drying agent and concentration gave a crude product, which was purified by silica gel chromatography on a Biotage (40m) column to afford 2.15 g (62% yield) of 1,6-dimethyl-3-iodo-4-(trifluoromethyl)-2-pyridone as an amorphous white solid. EI-HRMS m/e calcd for $C_8H_7F_3INO$ (M^+) 316.9524, found 316.9527.

c) Preparation of N-[(1,1-dimethylethoxyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine methyl ester



$C_8H_7F_3INO$
Mol. Wt.: 317.05

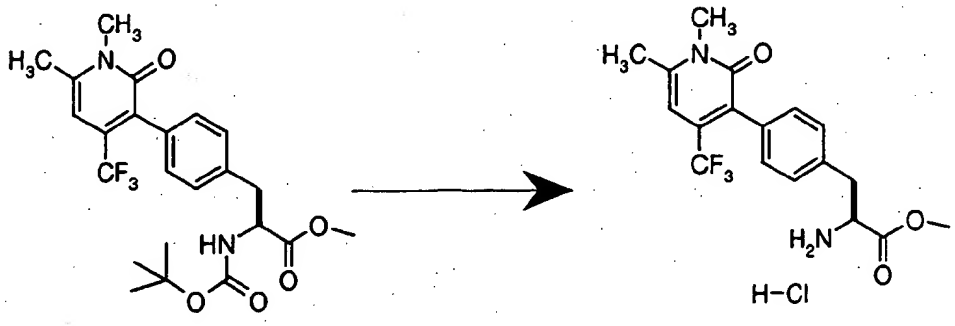
$C_{15}H_{20}INO_4$
Mol. Wt.: 405.23

$C_{23}H_{27}F_3N_2O_5$
Mol. Wt.: 468.47

To a suspension of zinc dust (1.96 g, 30 mmol) in THF (2.0 mL) was added 1,2-dibromoethane (172 µL, 2 mmol)) at room temperature. This suspension was heated to 60-65 °C with a heat gun until evolution of ethylene gas ceased. Then, the suspension was cooled to room temperature and trimethylchlorosilane (127 µL, 1 mmol)) was added and the mixture was stirred for 15 min. A suspension of 1,6-dimethyl-3-iodo-4-(trifluoromethyl)-2-pyridone (2.15 g, 6.78 mmol) in DMA (6 mL) was warmed with a heat gun to effect dissolution and was added in one portion to the reaction mixture. After addition, the mixture was heated to 70 °C and was stirred for 15 h, at which time the TLC analysis of an aliquot, which had been quenched with saturated ammonium chloride solution, indicated the absence of starting material. The reaction mixture was diluted with THF (6 mL), was cooled to room temperature and the excess zinc dust was allowed to settle.

The above prepared solution containing the zinc compound (6.78 mmol) was added to a solution of $Pd(dba)_2$ (108 mg, 0.2 mmol), trifurylphosphine (204 mg, 0.8 mmol) and N-[(1,1-dimethylethoxy)carbonyl]-4-iodo-L-phenylalanine methyl ester (1.62 g, 4 mmol) in THF (8 mL) at room temperature and the light yellow mixture was stirred for 15 h at 50 °C. The reaction mixture was poured into a saturated ammonium chloride solution and was extracted with ethyl acetate (3 x 70 mL). The combined extracts were washed with brine solution (150 mL) and were dried over anhydrous magnesium sulfate. Filtration of the drying agent and concentration gave the crude product, which was purified by silica gel chromatography on a Biotage (40m) column to obtain 0.711 g (38% yield) of N-[(1,1-dimethylethoxyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine methyl ester as an amorphous white solid. ES-HRMS m/e calcd for $C_{23}H_{27}F_3N_2O_5$ (M+Na) 491.1764, found 491.1770.

d) Preparation of 4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine methyl ester hydrochloride salt

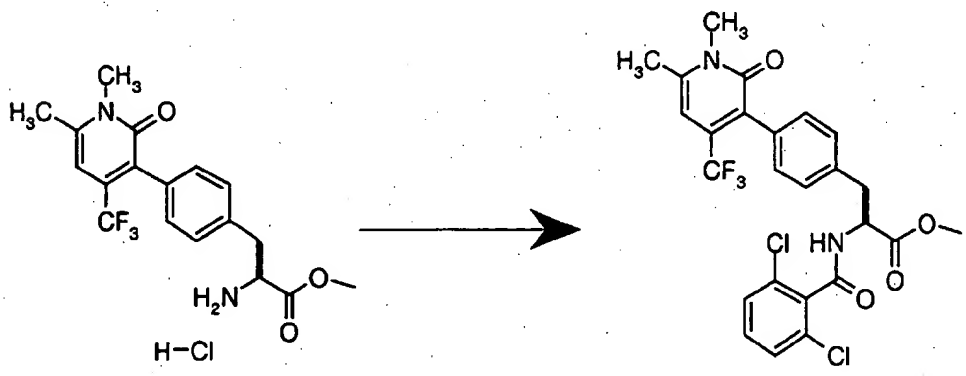


$C_{23}H_{27}F_3N_2O_5$
Mol. Wt.: 468.47

$C_{18}H_{20}ClF_3N_2O_3$
Mol. Wt.: 404.81

To a solution of N-[(1,1-dimethylethoxyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine methyl ester (132 mg, 0.33 mmol) in dioxane (3 mL) was added 4 N HCl solution in dioxane (4.5 mL) at room temperature. The solution was stirred for 4 h as a white solid was formed. The mixture was diluted with diethyl ether (50 mL) and solid was collected by filtration washing with diethyl ether. After drying under high vacuum, 315 mg (92% yield) of 4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine methyl ester hydrochloride salt was obtained as an amorphous white solid. ES-HRMS m/e calcd for $C_{18}H_{19}F_3N_2O_3$ (M+Na) 391.1241, found 391.1241.

e) Preparation of N-[(2,6-dichlorophenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine methyl ester



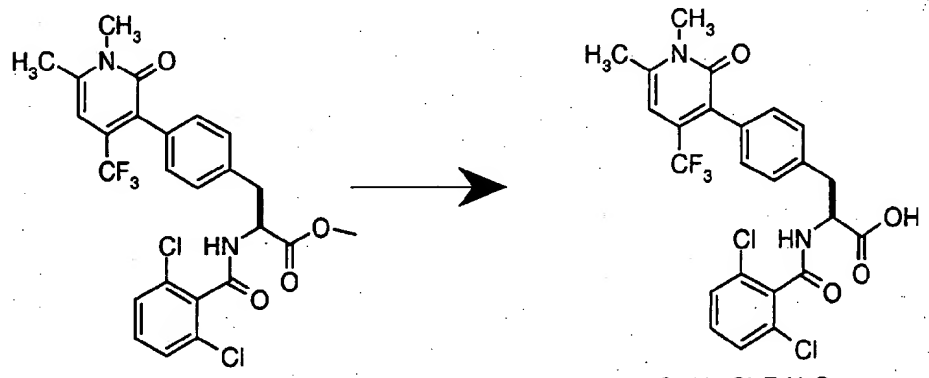
$C_{18}H_{20}ClF_3N_2O_3$
Mol. Wt.: 404.81

$C_{25}H_{21}Cl_2F_3N_2O_4$
Mol. Wt.: 541.35

To a suspension of 4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine methyl ester hydrochloride salt (150 mg, 0.37 mmol) and 2,6-

dichlorobenzoyl chloride (85 mg, 0.4 mmol) in dichloromethane (6 mL) was added DIEA (257 µL, 1.48 mmol) at room temperature. After 5 min, a clear solution was obtained which was stirred for 48 h. Then, the mixture was concentrated and the residue was dissolved in ethyl acetate (50 mL). The ethyl acetate solution was washed with 0.5 N HCl (50 mL), saturated $NaHCO_3$ solution (50 mL) and brine solution (50 mL) and was dried over anhydrous magnesium sulfate. Filtration of the drying agent and concentration gave crude product, which was purified by silica gel chromatography on a Biotage (40m) column to give 190 mg (95% yield) of N-[(2,6-dichlorophenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine methyl ester as an amorphous white solid. ES-HRMS m/e calcd for $C_{25}H_{21}Cl_2F_3N_2O_4$ (M+Na) 563.0724, found 563.0726.

f) Preparation of N-[(2,6-dichlorophenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine



$C_{25}H_{21}Cl_2F_3N_2O_4$
Mol. Wt.: 541.35

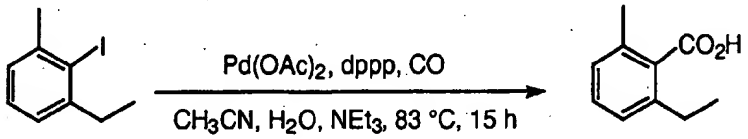
$C_{24}H_{19}Cl_2F_3N_2O_4$
Mol. Wt.: 527.32

To a suspension of N-[(2,6-dichlorophenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine methyl ester (177 mg, 0.326 mmol) in ethanol (6 mL) was added 1N aqueous sodium hydroxide solution (4 mL) at room temperature. The mixture was stirred for 5 h. Then, the ethanol was removed under vacuum and the residue was diluted with water (20 mL). The aqueous solution was washed with diethyl ether (50 mL) to remove any neutral impurities. The aqueous layer was acidified with 1.0 N HCl and the product was extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with brine solution (50 mL) and were dried over anhydrous magnesium sulfate. Filtration of the drying agent and concentration afforded 159 mg (92% yield) of N-[(2,6-dichlorophenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-

oxo-3-pyridinyl]-L-phenylalanine as a white solid: mp 238-240°C. ES-HRMS m/e calcd for $C_{24}H_{19}Cl_2F_3N_2O_4$ (M+Na) 549.0567, found 549.0570.

Example 34. Preparation of N-[(2-ethyl-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine

a. Preparation of 2-ethyl-6-methylbenzoic acid.



$C_9H_{11}I$
Mol. Wt.: 246.09

$C_{10}H_{12}O_2$
Mol. Wt.: 164.20

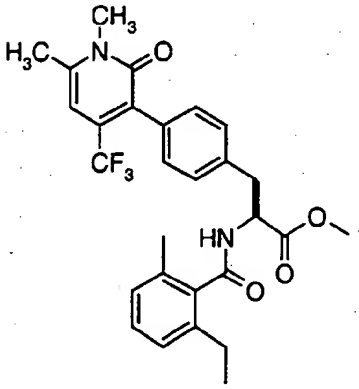
A 250 mL pressure bottle was charged with 2-ethyl-6-methyliodobenzene (30.07 mmol, 7.4 g), $Pd(OAc)_2$ (1.43 mmol, 334 mg) and dppp (1.43 mmol, 620 mg). The flask was closed with a septum and evacuated three times with argon. Then, acetonitrile (96 mL), triethylamine (189 mmol, 19.0 g, 26.25 mL) and water (19.1 mL) were added successively by the aid of syringe and the rubber septum was replaced with teflon lined cap connected to a carbon monoxide source. The flask was now pressurized with carbon monoxide (40 psi) and the excess pressure was released. This process was repeated three times and finally the mixture was stirred for 5 min under 40 psi carbon monoxide pressure. The flask was then disconnected from the carbon monoxide cylinder and immersed in a preheated oil bath (83-85 °C). The reaction mixture turned black over 1 hr and was stirred for another 14 hr at this temperature. Then, the reaction mixture was cooled to room temperature and the pressure was released. The resulting mixture was diluted with ether (200 mL) and 1.0N NaOH (20 mL). The formed acid was extracted into water (2 x 100 mL). The combined water extracts were neutralized with 1.0N HCl and the acid was extracted into dichloromethane (3 x 100 mL). The combined dichloromethane extracts were washed with brine solution and dried over $MgSO_4$. Filtration of the drying agent and removal of solvent under vacuum gave 3.58 g (72.5%) of a viscous brown oil which slowly solidfied overnight. HR MS: Obs. mass, 164.0833. Calcd. mass, 164.0837 (M+).

b. Preparation of 2-ethyl-6-methylbenzoyl chloride

Molecular Weight = 182.65
Molecular Formula = C10H11ClO

A solution of 2-ethyl-6-methylbenzoic acid (49 mg, 0.30 mmol) in dichloromethane (3 mL) containing DMF (1 drop) was treated with oxalyl chloride (0.14 mL, 1.6 mmol) and the mixture was stirred for 15 h. The mixture was concentrated, azeotroping with toluene to remove traces of oxalyl chloride and the residue was used directly in the next step.

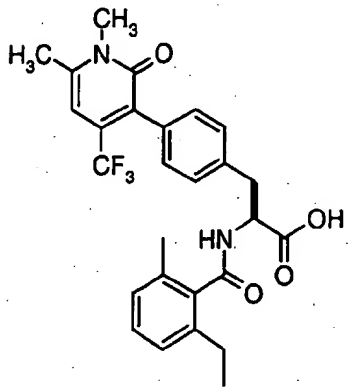
c. Preparation of N-[(2-ethyl-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine methyl ester



Molecular Weight = 514.54
Molecular Formula = C28H29F3N2O4

A mixture of the above prepared acid chloride, 4-(1,3-dimethyl-2,4-dioxo-6-(trifluoromethyl)-5-pyrimidinyl)-L-phenylalanine (100 mg, 0.25 mmol) in dichloromethane (5 mL) was treated with DIPEA (0.17 mL, 1.0 mmol) and the resulting light brown solution was stirred for 3 days. The mixture was concentrated, diluted with ethyl acetate, washed with 1 N HCl and brine solution and was dried over magnesium sulfate. Filtration and evaporation afforded a residue, which was purified by silica gel chromatography using a Biotage column (40s) to give N-[(2-ethyl-6-methylphenyl)carbonyl]-4-[1,3-dimethy-2,4-dioxo-6-(trifluoromethyl)-5-pyrimidinyl]-L-phenylalanine methyl ester as a white foam (79 mg, 62%). ES-HRMS m/e calcd for $C_{28}H_{29}F_3NO_4$ (M+Na) 537.1974, found 537.1972.

d. Preparation of N-[(2-ethyl-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine

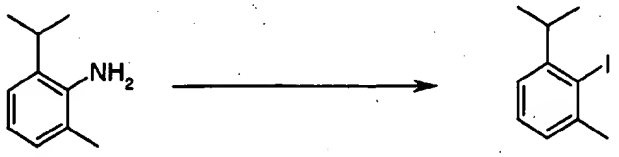


$C_{27}H_{27}F_3N_2O_4$
Mol. Wt.: 500.51

A solution of N-[(2-ethyl-6-methylphenyl)carbonyl]-4-(1,3-dimethy-2,4-dioxo-6-(trifluoromethyl)-5-pyrimidinyl)-L-phenylalanine methyl ester (74 mg, 0.14 mmol), and 1 N sodium hydroxide (2 mL, 2 mmol) in ethanol (3 mL) was heated to 40-45 C for 3 h. Then, the ethanol was removed under vacuum and the residue was diluted with water. The aqueous solution was washed with diethyl ether to remove any neutral impurities. The aqueous layer was acidified with 1.0 N HCl and the product was extracted with ethyl acetate. The combined organic extracts were washed with brine solution and were dried over anhydrous magnesium sulfate. Filtration of the drying agent and concentration afforded 68 mg (95% yield) of N-[(2-ethyl-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine (mp 219-221°C). ES-HRMS m/e calcd for $C_{27}H_{27}F_3N_2O_4$ (M+Na) 523.1815, found 523.1816.

Example 35. Preparation of N-[(2-(1-methylethyl)-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine

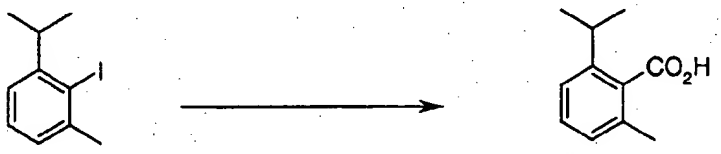
a). Preparation of 2-(1-methylethyl)-6-methyliodobenzene



Molecular Weight = 260.11
Molecular Formula = C10H13I

To a suspension of 2-(1-methylethyl)-6-methylaniline (15.57 mmol, 14.9 g), in conc. HCl (50 mL) and 30 g of ice, was added dropwise a solution of $NaNO_2$ (110 mmol, 8 g) in H_2O (35 mL) at -5 °C to 5 °C for 30 min. After addition, the red colored solution was stirred for another 30 min. Then, a solution of KI (200 mmol, 33.2 g) in H_2O (50 mL) was added dropwise over 20 min at 0-5 °C. After the addition, the mixture was allowed to warm to room temperature during which time, an exothermic reaction with gas evolution occurred. The resulting red colored solution was stirred for 18 h. Then, the mixture was extracted with ethyl acetate (3 x 100 mL). The combined extracts were washed with sodium thiosulfate solution (200 mL), brine solution and dried over $MgSO_4$. Filtration of the drying agent and concentration of the solvent under vacuum gave a colored compound which was purified by a silica gel column chromatography to obtain pure 2-(1-methylethyl)-6-methyliodobenzene (17.8 g, 68%) as a yellow oil. HR MS: Obs. mass, 260.0063. Calcd. mass, 260.0062 (M+).

b) Preparation of 2-(1-methylethyl)-6-methylbenzoic acid.



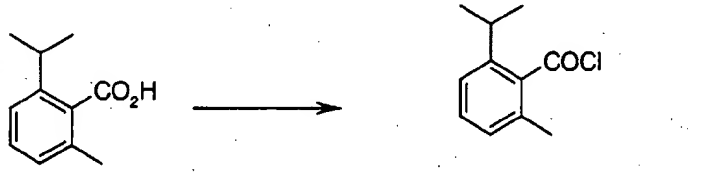
Molecular Weight = 260.11
Molecular Formula = C10H13I

Molecular Weight = 178.23
Molecular Formula = C11H14O2

A 250 mL pressure bottle was charged with 2-(1-methylethyl)-6-methyliodobenzene (25.2 mmol, 6.55 g), $Pd(OAc)_2$ (1.2 mmol, 280 mg) and dppp (1.2 mmol, 520 mg). The flask was closed with a septum and evacuated three times with argon. Then, acetonitrile (96 mL), triethylamine (188.7 mmol, 19.0 g, 26.25 mL) and water (19.1 mL) were added successively by the aid of syringe. Then, the

rubber septum was replaced with teflon lined cap connected to a carbon monoxide source. The flask was now pressurized with carbon monoxide (40 psi) and the excess pressure was released. This process was repeated three times and finally the mixture was stirred for 5 min under 40 psi carbon monoxide pressure. The flask was then disconnected from the carbon monoxide cylinder and immersed in a preheated oil bath (83-85 °C). The reaction mixture turned black in 1 hr and was stirred for another 4 hr at this temperature. Then, the reaction mixture was cooled to room temperature, the pressure was released and the mixture was diluted with ether (200 mL) and 1.0N NaOH (10 mL). The acid was extracted into water (2 x 100 mL). The combined aqueous extracts were neutralized with 1.0N HCl and the acid was extracted into ethyl acetate (2 x 100 mL). The combined organic extracts were washed with brine solution and dried over $MgSO_4$. Filtration of the drying agent and concentration gave 2.8 g (62%) of a viscous yellow oil. HR MS: Obs. mass, 178.0996. Calcd. mass, 178.0994 (M+).

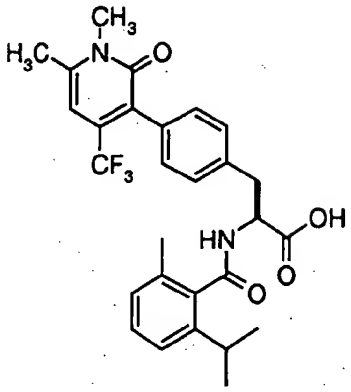
c. Preparation of 2-(1-methylethyl)-6-methylbenzoyl chloride



Molecular Weight = 196.68
Molecular Formula = C11H13ClO

A solution of 2-(1-methylethyl)-6-methylbenzoic acid (64 mg, 0.35 mmol) in dichloromethane (3 mL) containing DMF (2 drops) was treated with oxalyl chloride (0.16 mL, 1.8 mmol) and the mixture was stirred for 15 h. The mixture was concentrated, azeotroping with toluene to remove traces of oxalyl chloride and the residue was used directly in the next step.

d. Preparation of N-[[2-(1-methylethyl)-6-methylphenyl]carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine

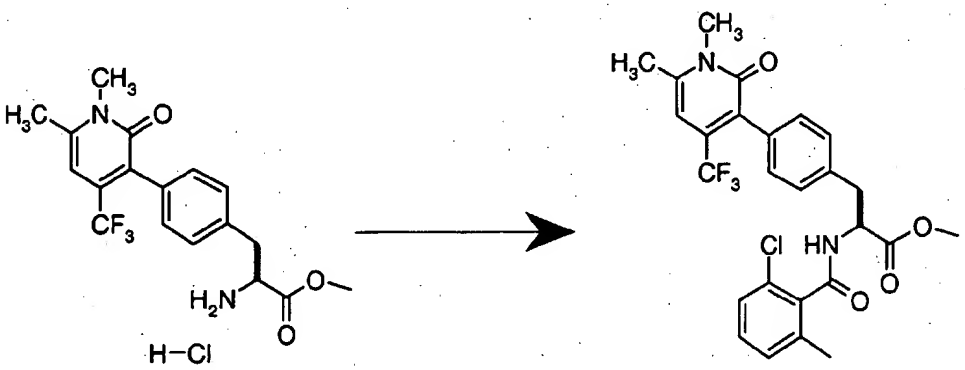


$C_{28}H_{29}F_3N_2O_4$
Mol. Wt.: 514.54

N-[[2-(1-methylethyl)-6-methylphenyl]carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine was prepared from 4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine methyl ester and 2-(1-methylethyl)-6-methylbenzoyl chloride using the general procedures described in example 33. ES-HRMS m/e calcd for $C_{28}H_{29}F_3N_2O_4$ (M+Na) 537.1972, found 537.1977.

Example 36. Preparation of N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine

a) Preparation of N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine methyl ester



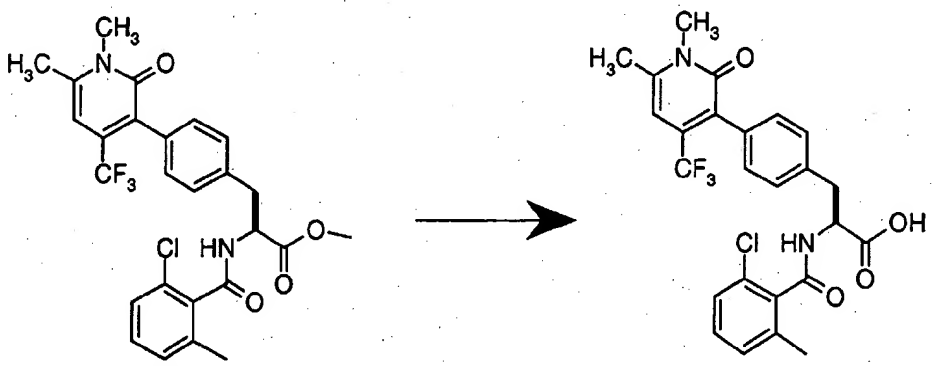
$C_{18}H_{20}ClF_3N_2O_3$
Mol. Wt.: 404.81

$C_{26}H_{24}ClF_3N_2O_4$
Mol. Wt.: 520.93

To a suspension of 4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine methyl ester hydrochloride salt (100 mg, 0.25 mmol), 2-chloro-6-methylbenzoic acid (60 mg, 0.35 mmol) and HBTU (132 mg, 0.35 mmol) in DMF (2 mL) was added DIEA (174 μL, 1.0 mmol) at room temperature. The resulting

mixture was stirred for 72 h. Then, the mixture was poured into water (25 mL) and was extracted with ethyl acetate (2 x 15 mL). The combined ethyl acetate extracts were washed successively with 0.5 N HCl (25 mL), saturated $NaHCO_3$ solution (25 mL), brine solution (25 mL) and were dried over anhydrous magnesium sulfate. Filtration of the drying agent and concentration gave the crude product which was purified by silica gel chromatography using a Biotage (40s) column to afford 98 mg (75% yield) of N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine methyl ester as an amorphous white solid. ES-HRMS m/e calcd for $C_{26}H_{24}ClF_3N_2O_4$ (M+Na) 543.1268, found 543.1275.

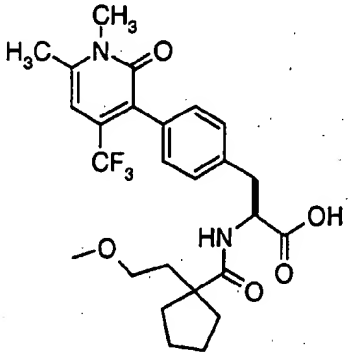
b) Preparation of N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine



To a suspension of N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine methyl ester (91 mg, 0.174 mmol) in ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (4 mL) at room temperature. The resulting solution was heated to 40-45 °C and stirred for 4 h. Then, the ethanol was removed under vacuum and the residue was diluted with water (25 mL). The aqueous solution was washed with diethyl ether (25 mL) to remove any neutral impurities. The aqueous layer was acidified with 1.0 N HCl and was extracted with ethyl acetate (2 x 25 mL). The combined organic extracts were washed with brine solution (50 mL) and were dried over anhydrous magnesium sulfate. Filtration of the drying agent and concentration of the filtrate afforded 71 mg (80% yield) of N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine as a white solid:

mp 220-223°C. ES-HRMS m/e calcd for $C_{25}H_{22}ClF_3N_2O_4$ (M+Na) 529.1111, found 529.1119.

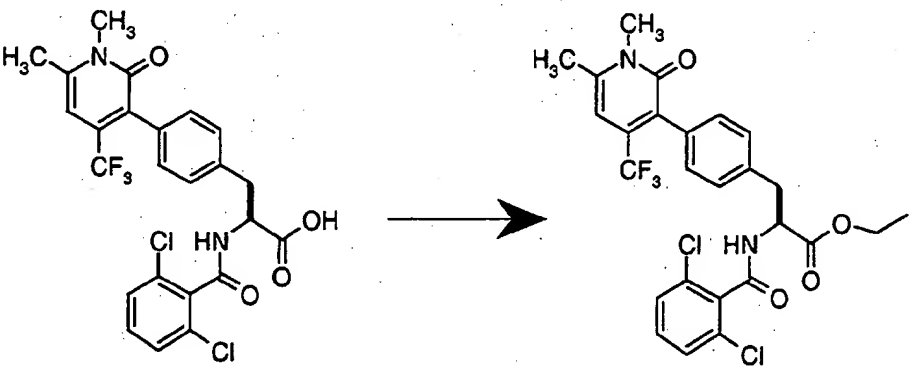
Example 37. Preparation of N-[[1-(2-methoxyethyl)cyclopentyl]carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine



$C_{26}H_{31}F_3N_2O_5$
Mol. Wt.: 508.53

N-[[1-(2-methoxyethyl)cyclopentyl]carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine (mp 181-183°C) was prepared from 4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine methyl ester and 1-(2-methoxyethyl)cyclopentane carboxylic acid (obtained as described in WO 9910313) using the general procedures described in example 36. ES-HRMS m/e calcd for $C_{26}H_{31}F_3N_2O_5$ (M+Na) 531.2077, found 531.2084.

Example 38. Preparation of N-[(2,6-dichlorophenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine ethyl ester



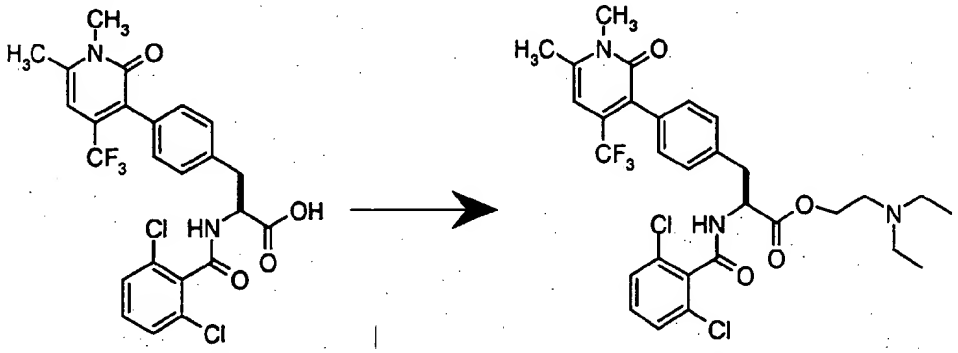
$C_{24}H_{19}Cl_2F_3N_2O_4$
Mol. Wt.: 527.32

$C_{26}H_{23}Cl_2F_3N_2O_4$
Mol. Wt.: 555.37

To a suspension of N-[(2,6-dichlorophenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine (145 mg, 0.275 mmol) and

sodium bicarbonate (185 mg, 2.2 mmol) in DMF (2 mL) was added iodoethane (343 mg, 2.2 mmol) at room temperature. The mixture was stirred for 72 h at room temperature. Then, the reaction mixture was poured into water (30 mL) and was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with brine solution (60 mL) and were dried over anhydrous magnesium sulfate. Filtration of the drying agent and concentration of the filtrate gave 129 mg (85% yield) of N-[(2,6-dichlorophenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine ethyl ester as a crystalline white solid: mp 86-91°C. ES-HRMS m/e calcd for $C_{26}H_{23}Cl_2F_3N_2O_4$ (M+Na) 577.0876, found 577.0887.

Example 39. Preparation of N-[(2,6-dichlorophenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 2-[(N,N-diethyl)amino]ethyl ester



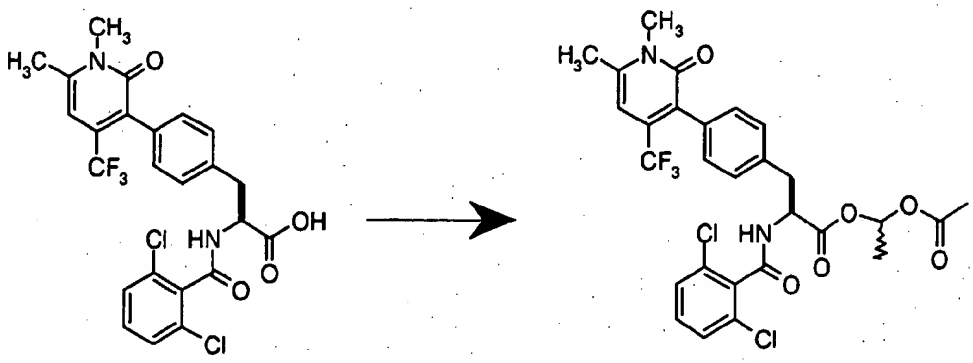
$C_{24}H_{19}Cl_2F_3N_2O_4$
Mol. Wt.: 527.32

$C_{30}H_{32}Cl_2F_3N_3O_4$
Mol. Wt.: 626.49

To a mixture of N-[(2,6-dichlorophenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine (145 mg, 0.275 mmol), 2-diethylaminoethyl chloride hydrochloride (487 mg, 2.75 mmol) and potassium carbonate (380 mg, 2.7 mmol) was added ethyl acetate (3 mL) and water (3 mL) at room temperature. The mixture was stirred for 72 h at room temperature. Then, the reaction mixture was poured into a mixture of water (30 mL) and ethyl acetate (30 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were washed with brine solution (60 mL) and were dried over anhydrous magnesium sulfate. Filtration of the drying agent and concentration gave the crude product, which was purified by silica gel chromatography using a Biotage (40s) column afforded 122 mg (71% yield) of N-[(2,6-dichlorophenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 2-[(N,N-diethyl)amino]ethyl ester as an

amorphous white solid. ES-HRMS m/e calcd for $C_{30}H_{32}Cl_2F_3N_3O_4$ (M+H) 626.1796, found 626.1802.

Example 40. Preparation of N-[(2,6-dichlorophenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 1-(acetoxy)ethyl ester

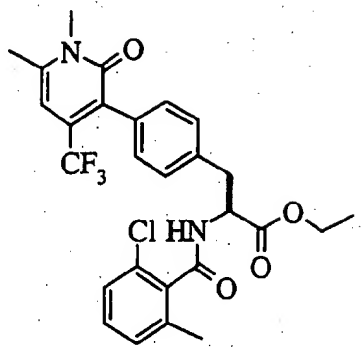


$C_{24}H_{19}Cl_2F_3N_2O_4$
Mol. Wt.: 527.32

$C_{28}H_{25}Cl_2F_3N_2O_6$
Mol. Wt.: 613.41

To a suspension of N-[(2,6-dichlorophenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine (145 mg, 0.275 mmol) and sodium bicarbonate (185 mg, 2.2 mmol) in DMF (2 mL) was added 1-chloroethyl acetate (270 mg, 2.2 mmol) at room temperature. The mixture was stirred for 48 h at room temperature. Then, the reaction mixture was poured into water (30 mL) and was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with brine solution (60 mL) and were dried over anhydrous magnesium sulfate. Filtration of the drying agent and concentration gave the crude product, which was purified by silica gel chromatography using a Biotage (40s) column to afford 110 mg (65% yield) of N-[(2,6-dichlorophenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 1-(acetoxy)ethyl ester as an amorphous white solid. ES-HRMS m/e calcd for $C_{28}H_{25}Cl_2F_3N_2O_6$ (M+Na) 635.0931, found 635.0932.

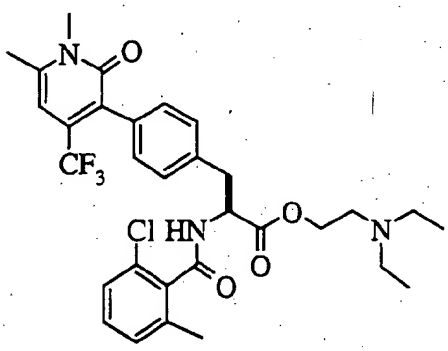
Example 41. Preparation of N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine ethyl ester



$C_{27}H_{26}ClF_3N_2O_4$
Mol. Wt.: 534.95

N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine ethyl ester can be prepared from N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine and iodoethane using the general procedure described in example 38.

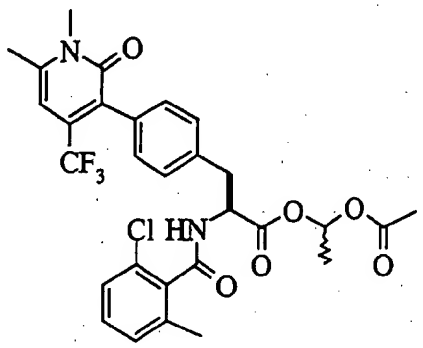
Example 42. Preparation of N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 2-[(N,N-diethyl)amino]ethyl ester



$C_{31}H_{35}ClF_3N_3O_4$
Mol. Wt.: 606.08

N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 2-[(N,N-diethyl)amino]ethyl ester can be prepared from N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine and 2-[(N,N-diethyl)amino]ethyl chloride hydrochloride using the general procedure described in example 39.

Example 43. Preparation of N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 1-(acetoxy)ethyl ester

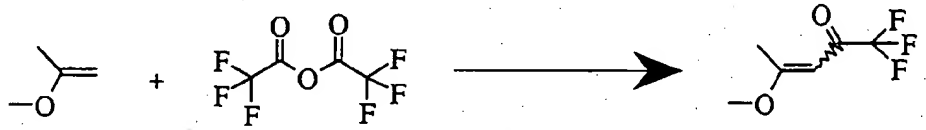


$C_{29}H_{28}ClF_3N_2O_6$
Mol. Wt.: 592.99

N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 1-(acetoxy)ethyl ester can be prepared from N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine and 1-chloroethyl acetate using the general procedure described in example 40.

Example 44. Preparation of N-[(2,6-dichlorophenyl)carbonyl]-4-(1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl)-L-phenylalanine

a) Preparation of 4-methoxy-1,1,1-trifluoropent-3-en-2-one



C_4H_8O
Mol. Wt.: 72.11

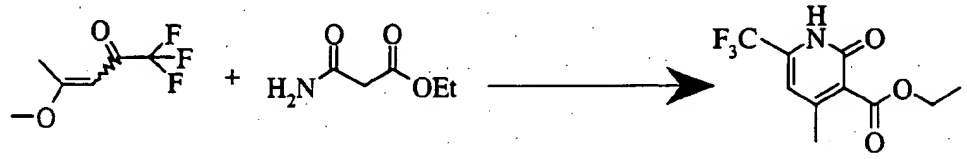
$C_4F_6O_3$
Mol. Wt.: 210.03

$C_6H_7F_3O_2$
Mol. Wt.: 168.11

To a solution of 2-methoxypropene (3.68 g, 51.03 mmol) and pyridine (1.35 g, 16.69 mmol) in dichloromethane (15 mL) was added a solution of trifluoroacetic anhydride (10 mL, 46.56 mmol) in dichloromethane (8 mL) at 0°C over a period of 10-12 min. After addition, the solution turned to dark red-brown and then the cooling bath was removed and stirring was stopped. The mixture was allowed to stand for 16 h and was diluted with ice cold water (45 mL) and dichloromethane (120 mL). The two layers were separated and the organic layer was washed successively with 2N HCl (35 mL), saturated sodium carbonate solution (75 mL)

and brine solution (25 mL) and was dried over anhydrous sodium sulfate. Filtration of the drying agent and concentration gave the crude product, which was purified by distillation under high vacuum to afford 5.546 g (65% yield) of 4-methoxy-1,1,1-trifluoropent-3-en-2-one as a light yellow oil.

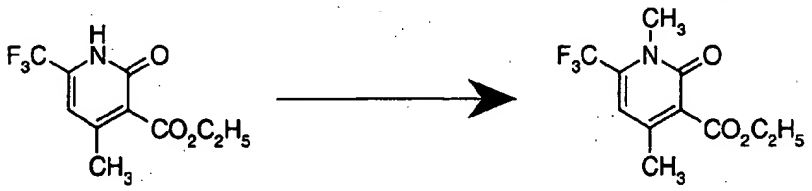
b) Preparation of 4-methyl-2(1H)-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid ethyl ester



$C_6H_7F_3O_2$ Mol. Wt.: 168.11 | $C_5H_9NO_3$ Mol. Wt.: 131.13 | $C_{10}H_{10}F_3NO_3$ Mol. Wt.: 249.19

To a suspension of 4-methoxy-1,1,1-trifluoropent-3-en-2-one (5.53 g, 32.89 mmol) and ethyl malonate monoamide (4.31 g, 32.89 mmol) in ethanol (30 mL) was added sodium ethoxide (11.72 g, 36.18 mmol, 21% pure) at room temperature and the reaction mixture was heated to ~85°C. After stirring for 18 h, the reaction mixture was cooled to room temperature and 15% HCl (10 mL) was added. Then, it was diluted with water (10 mL) and was extracted with chloroform (2 x 50 mL). The combined extracts were washed with brine solution (100 mL) and were dried over anhydrous sodium sulfate. Filtration of the drying agent and concentration gave the crude product, which was purified by silica gel chromatography on a Biotage (40m) column to afford 5.22 g (62% yield) of 4-methyl-2(1H)-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid ethyl ester as an amorphous white solid. ES-LRMS: m/z 313.4 ($M+Na+CH_3CN$).

c. Preparation of 1,4-dimethyl-2(1H)-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid ethyl ester

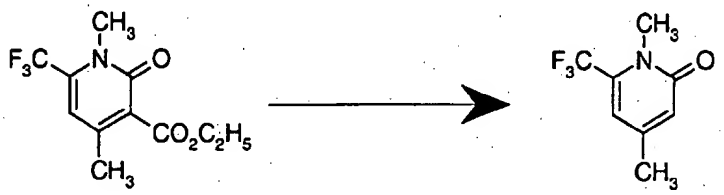


$C_{10}H_{10}F_3NO_3$ Mol. Wt.: 249.19 | $C_{11}H_{12}F_3NO_3$ Mol. Wt.: 263.22

To a suspension of 4-methyl-2(1H)-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid ethyl ester (5.2 g, 20.87 mmol) and potassium carbonate (8.65 g, 62.59 mmol)

in DME (50 mL) was added iodomethane (12 mL, 192.8 mmol) at room temperature and the reaction mixture was heated to reflux for 18 h. The reaction mixture was cooled to room temperature and the inorganic solids were filtered and the solids were washed with DME. The solvent was concentrated under vacuum and the residue was purified by silica gel chromatography on a Biotage (40m) column to afford 4.02 g (71% yield) of 1,4-dimethyl-2(1H)-oxo-6-(trifluoromethyl)pyridine 3-carboxylic acid ethyl ester as an amorphous white solid. ES-HRMS m/e calcd for $C_{11}H_{12}F_3NO_3$ (M+Na) 286.0661, found 286.0664.

d) Preparation of 1,4-dimethyl-6-(trifluoromethyl)-1H-pyridin-2-one

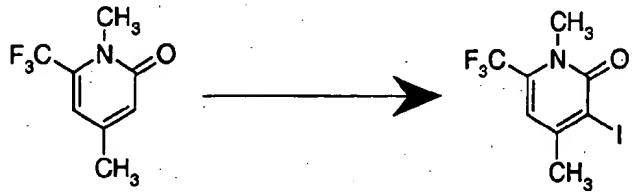


$C_{11}H_{12}F_3NO_3$
Mol. Wt.: 263.22

$C_8H_8F_3NO$
Mol. Wt.: 191.15

To a mixture of 1,4-dimethyl-2(1H)-oxo-6-(trifluoromethyl)pyridine-3-carboxylic acid ethyl ester (2.5 g, 9.5 mmol) and lithium chloride (1.0 g, 23.6 mmol) was added DMF (15 mL) and water (0.38 mL) at room temperature. The reaction mixture was heated to a bath temperature of 160°C and stirred for 19 h. The reaction mixture was cooled to room temperature and diluted with cold ethyl acetate and diethyl ether (75 mL, 1:1). The resulting mixture was washed with cold water (3 x 20 mL) and brine solution (20 mL) and was dried over anhydrous sodium sulfate. Filtration of the drying agent and concentration of the solvent gave the crude product, which was purified by silica gel chromatography on a Biotage (40s) column to afford 1.45 g (80% yield) of 1,4-dimethyl-6-(trifluoromethyl)-1H-pyridin-2-one as a light yellow solid. ES-HRMS m/e calcd for $C_8H_8F_3NO$ (M+H) 192.0631, found 192.0632.

e) Preparation of 1,4-dimethyl-3-iodo-6-(trifluoromethyl)-1H-pyridin-2-one

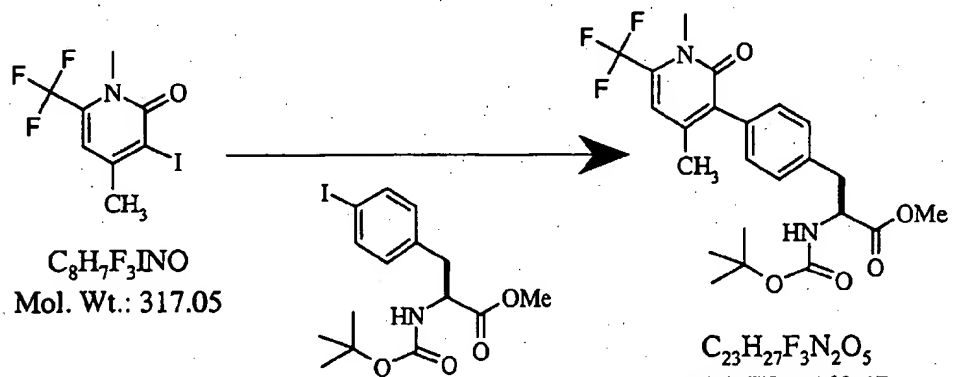


$C_8H_8F_3NO$
Mol. Wt.: 191.15

$C_8H_7F_3INO$
Mol. Wt.: 317.04

To a solution of 1,4-dimethyl-6-(trifluoromethyl)-1H-pyridin-2-one (1.44 g, 7.23 mmol), trifluoroacetic acid (9 mL) and trifluoroacetic anhydride (1.53 mL, 10.85 mmol) was added NIS (2.569 g, 10.85 mmol) at room temperature. Then, the mixture was heated to 70-85°C and was stirred for 2 h. The reaction mixture was cooled to room temperature and saturated sodium carbonate solution was added slowly to neutralize the solution. Then, the aqueous mixture was extracted with ethyl acetate (2 x 50 mL). The combined extracts were washed successively with saturated sodium thiosulfate solution (100 mL) and brine solution (100 mL) and were dried over anhydrous sodium sulfate. Filtration of the drying agent and concentration of the solvent gave a crude product, which was purified by silica gel chromatography on a Biotage (40m) column to afford 1.02 g (45% yield) of 1,4-dimethyl-3-iodo-6-(trifluoromethyl)-1H-pyridin-2-one as an amorphous white solid. ES-LRMS: m/z 318.1 (M+H), 381.2 (M+Na+CH_3CN).

f) Preparation of N-[(1,1-dimethylethoxyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine methyl ester



$C_8H_7F_3INO$
Mol. Wt.: 317.05

$C_{15}H_{20}INO_4$
Mol. Wt.: 405.23

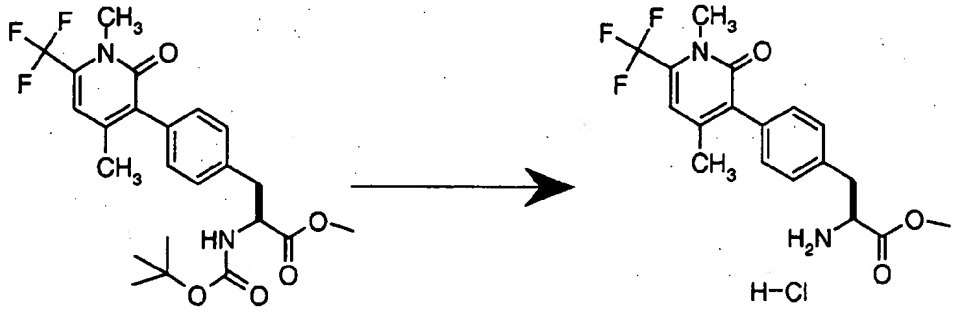
$C_{23}H_{27}F_3N_2O_5$
Mol. Wt.: 468.47

To a suspension of zinc dust (1.96 g, 30 mmol) in THF (1.0 mL) was added 1,2-dibromoethane (172 µL, 2 mmol)) at room temperature. This suspension was

heated to 60-65 °C with a heat gun until evolution of ethylene gas ceased. Then, the suspension was cooled to room temperature and trimethylchlorosilane (150 µL, 1.2 mmol)) was added and the mixture was stirred for 15 min. A suspension of 1,4-dimethyl-3-iodo-6-(trifluoromethyl)-2-pyridone (2.4 g, 7.57 mmol) in DMA (6 mL) was warmed with a heat gun to effect dissolution and was added in one portion to the reaction mixture. After addition, the mixture was heated to 70-75 °C and was stirred for 2 h, at which time the TLC analysis of an aliquot, which had been quenched with saturated ammonium chloride solution, indicated the absence of starting material. The reaction mixture was diluted with THF (5 mL), was cooled to room temperature and the excess zinc dust was allowed to settle.

The above prepared solution containing the zinc compound (7.57 mmol) was added to a solution of $Pd(dba)_2$ (274 mg, 0.478 mmol), trifurylphosphine (391 mg, 1.287 mmol) and N-[(1,1-dimethylethoxy)carbonyl]-4-iodo-L-phenylalanine methyl ester (3 g, 7.411 mmol) in THF (7 mL) at room temperature and the light yellow mixture was stirred for 40 h at 50-55 °C. The reaction mixture was poured into a saturated ammonium chloride solution and was extracted with ethyl acetate (3 x 70 mL). The combined extracts were washed with brine solution (100 mL) and were dried over anhydrous magnesium sulfate. Filtration of the drying agent and concentration gave the crude product, which was purified by silica gel chromatography on a Biotage (40m) column to obtain 1.289 g (36% yield) of N-[(1,1-dimethylethoxyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine methyl ester as an amorphous white solid. ES-HRMS m/e calcd for $C_{23}H_{27}F_3N_2O_5$ (M+Na) 491.1764, found 491.1764.

g) Preparation of 4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine methyl ester hydrochloride salt

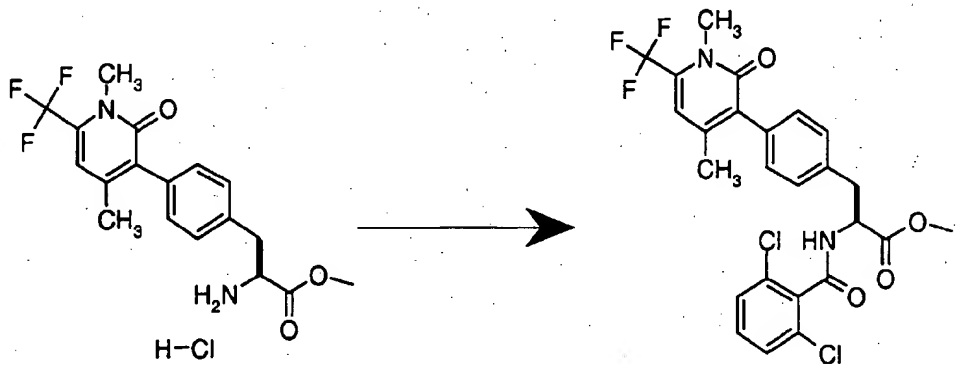


$C_{23}H_{27}F_3N_2O_5$
Mol. Wt.: 468.47

$C_{18}H_{20}ClF_3N_2O_3$
Mol. Wt.: 404.81

A N-[(1,1-dimethylethoxyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine methyl ester (253 mg, 0.54 mmol) was treated with 4 N HCl solution in dioxane (4.0 mL) at room temperature. The solution was stirred for 2 h as a white solid was formed. The mixture was concentrated and the residue was dissolved in methanol. After removal of methanol, the residue was dried under high vacuum to obtain 221 mg (100% yield) of 4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine methyl ester hydrochloride salt as an amorphous white solid. ES-LRMS m/z 369.3 (M+H), 410.3 (M+CH3CN).

h) Preparation of N-[(2,6-dichlorophenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine methyl ester



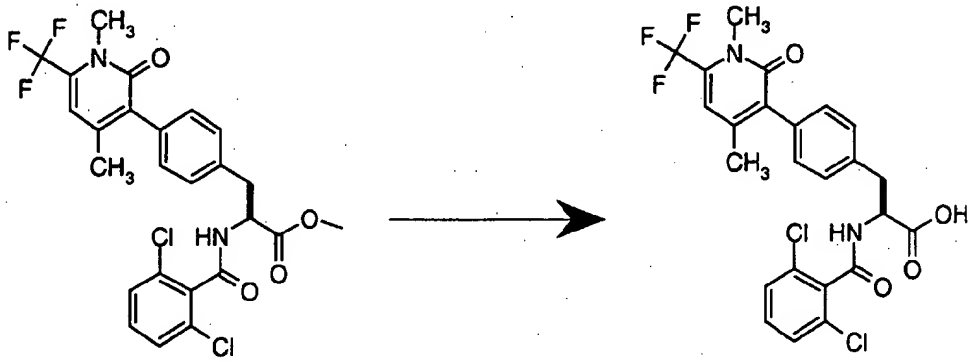
$C_{18}H_{20}ClF_3N_2O_3$
Mol. Wt.: 404.81

$C_{25}H_{21}Cl_2F_3N_2O_4$
Mol. Wt.: 541.35

To a suspension of 4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine methyl ester hydrochloride salt (216 mg, 0.53 mmol) and 2,6-dichlorobenzoyl chloride (120 mg, 0.57 mmol) in THF (6 mL) was added DIEA (210 µL, 1.19 mmol) at room temperature. After 5 min, a clear solution was obtained which was stirred for 18 h. Then, the mixture was diluted with ethyl acetate (50 mL). The ethyl acetate solution was washed successively with 0.5 N HCl (50 mL), saturated $NaHCO_3$ solution (50 mL) and brine solution (50 mL) and was dried over anhydrous magnesium sulfate. Filtration of the drying agent and concentration gave crude product, which was dissolved in ethyl acetate (~3 mL) and hexanes (~3-4 mL) was added and stored in the refrigerator. The solid was collected and washed with hexanes. After drying under high vacuum, 270 mg (93.5% yield) of N-[(2,6-dichlorophenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine methyl ester was obtained a

white solid: mp 170-173 °C. ES-HRMS m/e calcd for $C_{25}H_{21}Cl_2F_3N_2O_4$ (M+Na) 563.0724, found 563.0730.

i) Preparation of N-[(2,6-dichlorophenyl)carbonyl]-4-(1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl)-L-phenylalanine

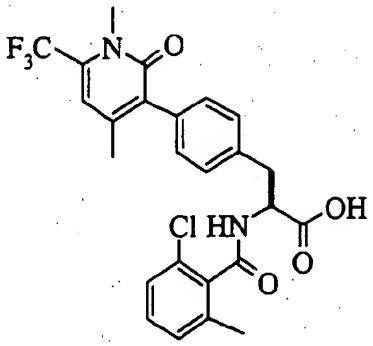


$C_{25}H_{21}Cl_2F_3N_2O_4$
Mol. Wt.: 541.35

$C_{24}H_{19}Cl_2F_3N_2O_4$
Mol. Wt.: 527.33

To a suspension of N-[(2,6-dichlorophenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine methyl ester (243 mg, 0.45 mmol) in ethanol (5 mL) was added 1N aqueous sodium hydroxide solution (1.8 mL) at room temperature. The mixture was heated to 45-50 °C and was stirred for 2 h. Then, the ethanol was removed under vacuum and the residue was diluted with water (20 mL). The aqueous solution was washed with ethyl acetate (50 mL) to remove any neutral impurities. The aqueous layer was acidified with 1.0 N HCl and the product was extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with brine solution (50 mL) and were dried over anhydrous magnesium sulfate. Filtration of the drying agent and concentration afforded 186 mg (79% yield) of N-[(2,6-dichlorophenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine as an amorphous white solid. ES-HRMS m/e calcd for $C_{24}H_{19}Cl_2F_3N_2O_4$ (M+Na) 549.0567, found 549.0573.

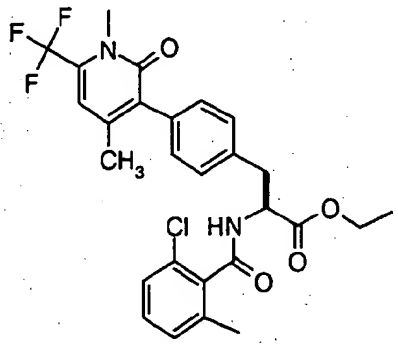
45. Preparation of N-[(2-chloro-6-methylphenyl)carbonyl]-4-(1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl)-L-phenylalanine



$C_{25}H_{22}ClF_3N_2O_4$
Mol. Wt.: 506.90

N-[(2-chloro-6-methylphenyl)carbonyl]-4-(1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl)-L-phenylalanine was prepared from 4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine methyl ester and 2-chloro-6-methylbenzoyl chloride using the general procedures described in example 44. ES-LRMS m/z 507.1 (M+H), 529.1 (M+Na).

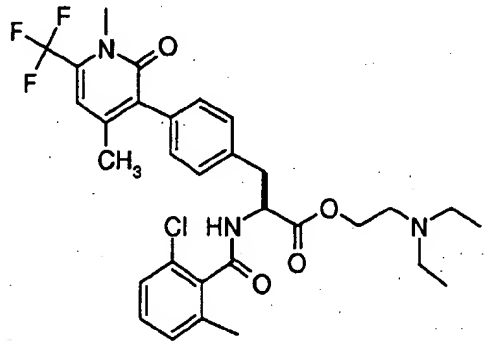
Example 46. Preparation of N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine ethyl ester



$C_{27}H_{26}ClF_3N_2O_4$
Mol. Wt.: 534.95

N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine ethyl ester can be prepared from N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine and iodoethane using the general procedure described in example 38.

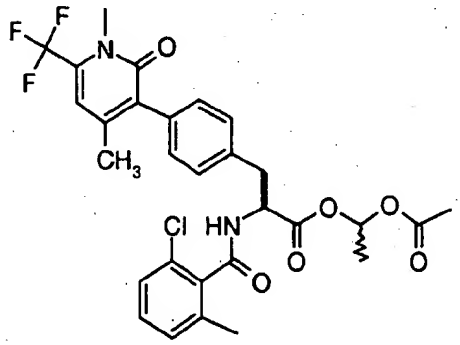
Example 47. Preparation of N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 2-[(N,N-diethyl)amino]ethyl ester



$C_{31}H_{35}ClF_3N_3O_4$
Mol. Wt.: 606.08

N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 2-[(N,N-diethyl)amino]ethyl ester can be prepared from N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine and 2-[(N,N-diethyl)amino]ethyl chloride hydrochloride using the general procedure described in example 39.

Example 48. Preparation of N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 1-(acetoxy)ethyl ester

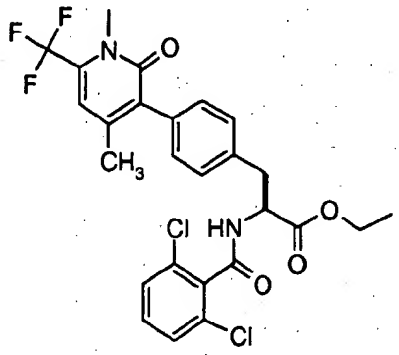


$C_{29}H_{28}ClF_3N_2O_6$
Mol. Wt.: 592.99

N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 1-(acetoxy)ethyl ester can be prepared from N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-

3-pyridinyl]-L-phenylalanine and 1-chloroethyl acetate using the general procedure described in example 40.

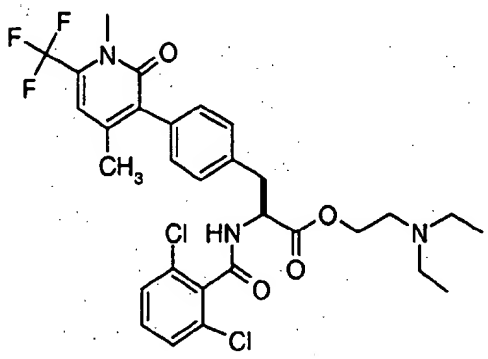
Example 49. Preparation of N-[(2,6-dichlorophenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine ethyl ester



$C_{26}H_{23}Cl_2F_3N_2O_4$
Mol. Wt.: 555.37

N-[(2,6-dichlorophenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine ethyl ester can be prepared from N-[(2,6-dichlorophenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine and iodoethane using the general procedure described in example 38.

Example 50. Preparation of N-[(2,6-dichlorophenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 2-[(N,N-diethyl)amino]ethyl ester

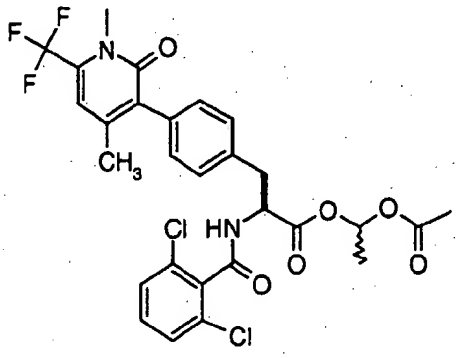


$C_{30}H_{32}Cl_2F_3N_3O_4$
Mol. Wt.: 626.49

N-[(2,6-dichlorophenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 2-[(N,N-diethyl)amino]ethyl ester can be prepared from N-[(2,6-dichlorophenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-

oxo-3-pyridinyl]-L-phenylalanine and 2-[(N,N-diethyl)amino]ethyl chloride hydrochloride using the general procedure described in example 39.

Example 51. Preparation of N-[(2,6-dichlorophenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 1-(acetoxy)ethyl ester



$C_{28}H_{25}Cl_2F_3N_2O_6$
Mol. Wt.: 613.41

N-[(2,6-dichlorophenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 1-(acetoxy)ethyl ester can be prepared from N-[(2,6-dichlorophenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine and 1-chloroethyl acetate using the general procedure described in example 40.

Bioassay Examples

Example A

VLA-4 / VCAM-1 Screening Assay

VLA-4 antagonist activity, defined as ability to compete for binding to immobilized VCAM-1, was quantitated using a solid-phase, dual antibody ELISA. VLA-4 ($\alpha 4\beta 1$ integrin) bound to VCAM-1 was detected by a complex of anti-integrin $\beta 1$ antibody: HRP-conjugated anti-mouse IgG: chromogenic substrate (K-Blue). Initially, this entailed coating 96 well plates (Nunc Maxisorp) with recombinant human VCAM-1 (0.4 µg in 100 µl PBS), sealing each plate and then allowing the plates to stand at 4°C for ~18 hr. The VCAM-coated plates were subsequently blocked with 250 µl of 1% BSA/0.02% NaN_3 to reduce non-specific binding. On the day of assay, all plates were washed twice with VCAM Assay Buffer (200 µl/well of 50 mM Tris-HCl, 100 mM NaCl, 1 mM $MnCl_2$, 0.05% Tween 20; pH 7.4). Test

compounds were dissolved in 100% DMSO and then diluted 1:20 in VCAM Assay Buffer supplemented with 1 mg/mL BSA (i.e., final DMSO = 5%). A series of 1:4 dilutions were performed to achieve a concentration range of 0.005 nM - 1.563 μM for each test compound. 100 μl per well of each dilution was added to the VCAM-coated plates, followed by 10 μl of Ramos cell-derived VLA-4. These plates were sequentially mixed on a platform shaker for 1 min, incubated for 2 hr at 37°C, and then washed four times with 200 μl/well VCAM Assay Buffer. 100 μl of mouse anti-human integrin β1 antibody was added to each well (0.6 μg/mL in VCAM Assay Buffer + 1 mg/mL BSA) and allowed to incubate for 1 hr at 37°C. At the conclusion of this incubation period, all plates were washed four times with VCAM Assay Buffer (200 μl/well). A corresponding second antibody, HRP-conjugated goat anti-mouse IgG (100 μl per well @ 1:800 dilution in VCAM Assay Buffer + 1 mg/mL BSA), was then added to each well, followed by a 1 hr incubation at room temperature and concluded by three washes (200μl/well) with VCAM Assay Buffer. Color development was initiated by addition of 100 μl K-Blue per well (15 min incubation, room temp) and terminated by addition of 100 μl Red Stop Buffer per well. All plates were then read in a UV/Vis spectrophotometer at 650 nM. Results were calculated as % inhibition of total binding (i.e., VLA-4 + VCAM-1 in the absence of test compound). The results are provided in the following Table I (A = IC_{50} < 1 nM, B = IC_{50} <10 nM):

Compound of Example	Activity in VCAM/VLA-4 ELISA Assay
8	A
10	B
15	B
17	B
24	A
28	A

Table I

Example B

Ramos (VLA-4) / VCAM-1 Cell-Based Screening Assay Protocol

Materials:

Soluble recombinant human VCAM-1 (mixture of 5- and 7-Ig domain) was purified from CHO cell culture media by immunoaffinity chromatography and maintained in a solution containing 0.1 M Tris-glycine (pH 7.5), 0.1 M NaCl, 5 mM EDTA, 1 mM PMSF, 0.02% 0.02% NaN_3 and 10 µg/mL leupeptin. Calcein-AM was purchased from Molecular Probes Inc.

Methods:

VLA-4 ($\alpha 4\beta 1$ integrin) antagonist activity, defined as ability to compete with cell-surface VLA-4 for binding to immobilized VCAM-1, was quantitated using a Ramos-VCAM-1 cell adhesion assay. Ramos cells bearing cell-surface VLA-4, were labeled with a fluorescent dye (Calcein-AM) and allowed to bind VCAM-1 in the presence or absence of test compounds. A reduction in fluorescence intensity associated with adherent cells (% inhibition) reflected competitive inhibition of VLA-4 mediated cell adhesion by the test compound.

Initially, this entailed coating 96 well plates (Nunc Maxisorp) with recombinant human VCAM-1 (100 ng in 100 µl PBS), sealing each plate and allowing the plates to stand at 4°C for □18 hr. The VCAM-coated plates were subsequently washed twice with 0.05% Tween-20 in PBS, and then blocked for 1hr (room temperature) with 200 µl of Blocking Buffer (1% BSA/0.02% thimerosal) to reduce non-specific binding. Following the incubation with Blocking Buffer, plates were inverted, blotted and the remaining buffer aspirated. Each plate was then washed with 300 µl PBS, inverted and the remaining PBS aspirated.

Test compounds were dissolved in 100% DMSO and then diluted 1:25 in VCAM Cell Adhesion Assay Buffer (4 mM $CaCl_2$, 4 mM $MgCl_2$ in 50 mM TRIS-HCl, pH 7.5) (final DMSO = 4%). A series of eight 1:4 dilutions were performed for each compound (general concentration range of 1 nM - 12,500 nM). 100 µl/well of each dilution was added to the VCAM-coated plates, followed by 100 µl of Ramos cells (200,000 cells/well in 1% BSA/PBS). Plates containing test compounds and Ramos cells were allowed to incubate for 45 min at room temperature, after which 165 µl/well PBS was added. Plates were inverted to remove non-adherent cells, blotted

and 300 µl/well PBS added. Plates were again inverted, blotted and the remaining buffer gently aspirated. 100 µl Lysis Buffer (0.1% SDS in 50 mM TRIS-HCl, pH 8.5) was added to each well and agitated for 2 min on a rotary shaking platform. The plates were then read for fluorescence intensity on a Cytofluor 2300 (Millipore) fluorecence measurement system (excitation = 485 nm, emission = 530 nm). The results are shown in the following table:

The results are provided in the following Table II (A = IC_{50} < 100 nM, B = IC_{50} <10000 nM, C = IC_{50} <5,000 nM):

Compound of Example	Activity in VCAM/VLA-4 Ramos Cell Assay
8	B
10	B
15	C
24	B
28	C
30	B
31	B
32	B
33	A
34	B
35	B
36	A
37	B

Table II

Example C

Alpha4-Beta7 Assay Protocol

Two weeks to one day prior to the assay, Nunc high-binding F96 Maxisorp immuno plates, #442404 or #439454, were coated with 25ng/well (0.25µg/ml) MadCAM in a volume of 100µl/well. The plates were covered with sealer and wrapped in saran wrap followed by incubation in the refrigerator for at least 24 hours. The coating buffer employed was: 10mM carbonate/bicarbonate buffer made up from: 0.8 g/L sodium carbonate and 1.55 g/L sodium bicarbonate adjusted to pH 9.6 with 1 N HCl.

Assay buffers consisted of the following:

Wash Buffer: 0.05% Tween 20 in PBS

Blocking Buffer: 1% Nonfat Dry Milk in PBS

Labeling Buffer: PBS

Cell Buffer: RPMI 1640 medium (no additives)

Binding Buffer: 1.5mM $CaCl_2$

0.5mM $MnCl_2$

50mM TRIS-HCl; add NaOH dropwise to pH 7.5

Bring to volume in H_2O

Adjust to pH 7.5

Dilution Buffer: 4% DMSO in Binding Buffer

Plates were washed 2X with wash buffer and then blocked at room temperature for at least 1 hour with Blocking Buffer. Sealed plates were sometimes blocked overnight in the refrigerator. Plates were then washed with PBS and hand blotted dry. Remaining liquid was aspirated from the wells.

Sufficient RPMI 8866 cells were removed from stock for assay (2 X 10^6 cells/ml x 10ml/plate x number of plates) and placed in a centrifuge tube. The tubes were filled to volume with PBS and were spun at 200 x G for 8 minutes. The buffer was poured off and the cells were resuspended to 10 X 10^6/ml in PBS and a stock solution of calcein in DMSO (5mg/mL) was added at 5µl/ml of cell suspension. The suspension was incubated for 30 minutes at 37° C in dark. The cells were then washed with PBS. The PBS was poured off and the cells resuspended in cell buffer at a concentration of 2 x 10^6 cells/mL for plating in the assay.

Stock solution of test compounds at 25 x first dilution desired in 100% DMSO were prepared. First dilutions for the standard, as well as test compounds, were 1:25 into straight Binding Buffer, while the remaining serial dilutions were into Dilution Buffer (Binding Buffer/4% DMSO). Stock concentrations and dilutions of compounds for screening were determined by anticipated activity.

For the assay, 129µl Binding Buffer was plated into first row of wells and 100µl Dilution Buffer was plated into remaining wells. A 5.4µl aliquot of each compound was pipetted into appropriate, labeled wells, in triplicate. The compounds were next diluted down the plate (34µl + 100µl => 4-fold dilution). For controls, 100µl of Dilution Buffer + 100µl Cell Buffer were plated into the nonspecific background wells (no cells, no compound) and 100µl Dilution Buffer + 100µl cells were plated into the total binding wells (no compound = 100% binding). Labeled cells at 2 X10^6

cells/ml, 100µl/well (= 2 X 10^5 cells/well) were added to each well containing compound. The plates were sealed and incubated in the dark for 45 minutes at room temperature. Following incubation, unbound cells were removed by adding 150µl PBS/well. The plates were inverted, blotted onto paper towels and washed by gently adding 200µl PBS to wells and blotting again. Remaining buffer was carefully aspirated from the wells. A final 100µl PBS was added to each well. The plates were then read for fluorescence intensity on a Cytofluor 2300 (Millipore) fluorecence measurement system (excitation = 485 nm, emission = 530 nm). IC_{50}s of each compound were determined by linear regression analysis. The results are shown in the following table:

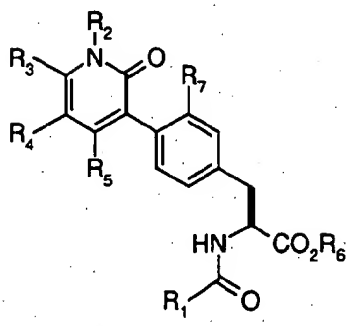
The results are provided in the following Table III :

Compound of Example	Activity in MadCAM/RPMI Cell Assay (A = IC_{50} < 100 nM, B = IC_{50} <10000 nM, C = IC_{50} <5,000 nM)
30	B
31	B
32	B
33	A
34	B
35	C
36	B
37	B

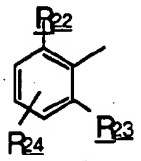
Table III

Claims

1. A compound of the formula:



wherein R_1 is a group of the formula Y-1

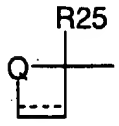


Y-1

wherein R_{22} and R_{23} are independently hydrogen, lower alkyl, lower alkoxy, cycloalkyl, aryl, arylalkyl, nitro, cyano, lower alkylthio, lower alkylsulfinyl, lower alkyl sulfonyl, lower alkanoyl, halogen, or perfluorolower alkyl and at least one of R_{22} and R_{23} is other than hydrogen, and R_{24} is hydrogen, lower alkyl, lower alkoxy, aryl, nitro, cyano, lower alkyl sulfonyl, or halogen; or

R_1 is a group of the formula Y-2, which is a five or six membered heteroaromatic ring bonded via a carbon atom to the amide carbonyl wherein said ring contains one, two or three heteroatoms selected from the group consisting of N, O and S and one or two atoms of said ring are independently substituted by lower alkyl, cycloalkyl, halogen, cyano, perfluoro lower alkyl, or aryl and at least one of said substituted atoms is adjacent to the carbon atom bonded to the amide carbonyl; or

R_1 is a group of the formula Y-3 which is a 3-7 membered ring of the formula:



Y-3

wherein R_{25} is lower alkyl, unsubstituted or fluorine substituted lower alkenyl, or a group of formula $R_{26}-(CH_2)_6-$, R_{26} is aryl, heteroaryl, azido, cyano, hydroxy,

lower alkoxy, lower alkoxycarbonyl, lower alkanoyl, lower alkylthio , lower alkyl sulfonyl, lower alkyl sulfinyl, perfluoro lower alkanoyl, nitro, or R_{26} is a group of formula $-NR_{28}R_{29}$, wherein R_{28} is hydrogen or lower alkyl, R_{29} is hydrogen, lower alkyl, lower alkoxycarbonyl, lower alkanoyl, aroyl, perfluoro lower alkanoylamino, lower alkyl sulfonyl, lower alkylaminocarbonyl, arylaminocarbonyl; or

R_{28} and R_{29}, taken together with the attached nitrogen atom, form a 4, 5 or 6-membered saturated heterocyclic ring optionally containing one additional heteroatom selected from O, S, and $N-R_{40}$.

Q is $-(CH_2)_f O-$, $-(CH_2)_f S-$, $-(CH_2)_f N(R_{27})-$, $-(CH_2)_f-$,

R_{27} is H, lower alkyl, aryl, lower alkanoyl, aroyl or lower alkoxycarbonyl,

R_{40} is H, lower alkyl, aryl, lower alkanoyl, aroyl or lower alkoxycarbonyl, the carbon atoms in the ring are unsubstituted or substituted by lower alkyl or halogen,

e is an integer from 0 to 4, and f is an integer from 0 to 3;

R_2 is hydrogen, lower alkyl, substituted lower alkyl, aryl, or aryl lower alkyl;

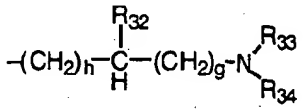
R_3 is hydrogen, halogen, lower alkyl, trifluoromethyl, or aryl;

R_4 is hydrogen, halogen, lower alkyl, or aryl;

R_5 is hydrogen, lower alkyl, lower alkoxy, or trifluoromethyl, or OH;

R_6 is hydrogen, lower alkyl, lower alkylcarbonyloxy lower alkyl,

or R_6 is a group of formula P-3:

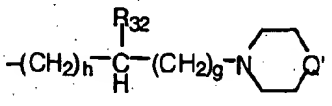


P-3

wherein:

R_{32} is hydrogen or lower alkyl; R_{33} is hydrogen, lower alkyl, aryl; R_{34} is hydrogen or lower alkyl; h is an integer from 0 to 2; g is an integer from 0 to 2; the sum of h and g is 1 to 3; or

R_6 is a group of formula P-4:



P-4

wherein: R_{32}, g, and h are as previously defined; Q' is O, S, $-(CH_2)_j-$, or a group of the formula N-R35; wherein R_{35} is hydrogen, lower alkyl, lower alkanoyl, lower alkoxycarbonyl; j is 0, 1 or 2; and

R_7 is hydrogen, chloro, lower alkoxy, or lower alkyl; or the pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 wherein R_3 is hydrogen, halogen, lower alkyl or aryl.

3. A compound of claim 1 or 2 wherein R_1 is Y-3 wherein Q is $-(CH_2)_f O-$, $-(CH_2)_f S-$, or, $-(CH_2)_f-$.

4. A compound of claim 3 wherein R_5 is hydrogen, lower alkyl, or trifluoromethyl.

5. A compound of claim 1 or claim 2 wherein R_1 is a group Y-1 wherein R_{22} and R_{23} are independently hydrogen, lower alkyl or halogen and R_{24} is hydrogen, lower alkyl or lower alkoxy.

6. A compound of claim 5 wherein R_{22} and R_{23} are independently hydrogen, lower alkyl or halogen, R_{24} is hydrogen or lower alkoxy and R_2 is aryl lower alkyl.

7. A compound of claim 1 or claim 2 wherein R_1 is a group of the formula Y-3 wherein R_{25} a group of formula $R_{26}-(CH_2)_e-$, wherein R_{26} is lower alkoxy, Q is $-(CH_2)_f-$, e is an integer from 0 to 4 and f is an integer from 0 to 3.

8. A compound of claim 1 or claim 2 wherein R_1 is a group of the formula Y-3 and R_2 is hydrogen, lower alkyl, substituted lower alkyl or aryl lower alkyl.

9. A compound of claim 8 wherein R_1 is a group of the formula Y-3 wherein R_{25} is a group of formula $R_{26}-(CH_2)_e-$, wherein R_{26} is lower alkoxy, Q is $-(CH_2)_f-$, e is an integer from 0 to 4, f is an integer from 0 to 3; and R_2 is aryl lower alkyl.

10. A compound of claim 1 or claim 2 wherein
R_2 is hydrogen, lower alkyl or aryl lower alkyl;
R_3 is hydrogen;

R_4 is hydrogen or halogen;
R_5 is hydrogen, lower alkyl, or trifluoromethyl, or lower alkoxy;
R_6 is hydrogen or lower alkyl; and
R_7 is hydrogen, chloro, lower alkoxy, or lower alkyl.

11. A compound of claim 10 wherein R_1 is a group of the formula Y-1.

12. A compound of claim 11 wherein R_1 is a group Y-1 wherein R_{22} and R_{23} are independently hydrogen, lower alkyl or halogen and R_{24} is hydrogen, lower alkyl or lower alkoxy.

13. A compound of claim 12 wherein R_1 is a group Y-1 wherein R_{24} is hydrogen and R_2 is aryl lower alkyl.

14. A compound of claim 10 wherein R_1 is Y-2.

15. A compound of claim 10 wherein R_1 is a group of the formula Y-3.

16. A compound of claim 15 wherein R_1 is a group of the formula Y-3 wherein R_{25} is a group of formula $R_{26}-(CH_2)_e-$, wherein R_{26} is lower alkoxy, Q is $-(CH_2)_f-$, e is an integer from 0 to 4 and f is an integer from 0 to 3.

17. A compound of claim 10 wherein
R_2 is hydrogen, lower alkyl or aryl lower alkyl;
R_3 is hydrogen;
R_4 is halogen;
R_5 is hydrogen;
R_6 is hydrogen or lower alkyl; and
R_7 is hydrogen, chloro, lower alkoxy, or lower alkyl.

18. A compound of any one of claims 1, 3 or 4, wherein R_1 is a group of formula Y-1 or a group of formula Y-3;
R_2 is hydrogen, lower alkyl or aryl lower alkyl;
R_3 is hydrogen, lower alkyl, or trifluoromethyl;
R_4 is hydrogen or halogen;

R_5 is hydrogen, lower alkyl, or trifluoromethyl;
R_6 is hydrogen, lower alkyl, lower alkylcarbonyloxy lower alkyl, a group of formula P-3 or a group of formula P-4; and
R_7 is hydrogen or lower alkyl.

19. A compound of claim 18 wherein
R_2 is lower alkyl or aryl lower alkyl;
R_6 is hydrogen, lower alkyl, lower alkylcarbonyloxy lower alkyl, or a group of formula P-3; and
R_7 is hydrogen.

20. A compound of claim 19 wherein R^1 is Y-1 wherein R_{22} and R_{23} are hydrogen, halogen or lower alkyl, R_{24} is hydrogen or lower alkoxy or R^1 is Y-3 wherein R_{25} is a group of formula $R_{26}-(CH_2)_e-$, wherein R_{26} is lower alkoxy, Q is $-(CH_2)_f-$, e is an integer from 0 to 4 and f is an integer from 0 to 3.

21. A compound of claim 20 wherein R_2 is lower alkyl, R_4 is hydrogen, and R_3 and R_5 are lower alkyl or trifluoromethyl.

22. A compound of claim 21 wherein R_6 is hydrogen.

23. A compound of claim 22 wherein R_1 is Y-1.

24. A compound of claim 23 wherein R_{22} and R_{23} are halogen or lower alkyl.

25. A compound of claim 24 which is
N-[(2,6-dichlorophenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine;
N-[(2-ethyl-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine;
N-[(2-(1-methylethyl)-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine;
N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine;

N-[(2,6-dichlorophenyl)carbonyl]-4-(1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl)-L-phenylalanine; or

N-[(2-chloro-6-methylphenyl)carbonyl]-4-(1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl)-L-phenylalanine.

26. A compound of claim 22 wherein R_1 is Y-3.

27. A compound of claim 26 which is N-[[1-(2-methoxyethyl)cyclopentyl]-carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine.

28. A compound of claim 21 wherein R_6 is lower alkyl.

29. A compound of claim 28 which is

N-[(2,6-dichlorophenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine ethyl ester;

N-[(2,6-dichlorophenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine ethyl ester;

N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine ethyl ester; or

N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine ethyl ester.

30. A compound of claim 21 wherein R_6 is lower alkylcarbonyloxy lower alkyl.

31. A compound of claim 30 which is

N-[(2,6-dichlorophenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 1-(acetoxy)ethyl ester;

N-[(2,6-dichlorophenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 1-(acetoxy)ethyl ester;

N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 1-(acetoxy)ethyl ester; or

N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 1-(acetoxy)ethyl ester.

32. A compound of claim 21 wherein R_6 is a group of formula P-3 wherein R_{32} is hydrogen; R_{33} and R_{34} are lower alkyl; one of g and h is 1 and the other is 0.

33. A compound of claim 32 which is

N-[(2,6-dichlorophenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 2-[(N,N-diethyl)amino]ethyl ester;

N-[(2,6-dichlorophenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 2-[(N,N-diethyl)amino]ethyl ester;

N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,6-dimethyl-4-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 2-[(N,N-diethyl)amino]ethyl ester; or

N-[(2-chloro-6-methylphenyl)carbonyl]-4-[1,4-dimethyl-6-(trifluoromethyl)-2-oxo-3-pyridinyl]-L-phenylalanine 2-[(N,N-diethyl)amino]ethyl ester.

34. A compound of claim 20 wherein R_6 is hydrogen.

35. A compound of claim 34 wherein R_2 is lower alkyl; R_3 is hydrogen; R_4 is hydrogen or halogen; and R_5 is hydrogen or lower alkyl.

36. A compound of claim 35 wherein R_1 is Y-1.

37. A compound of claim 36 wherein R_{22} and R_{23} are lower alkyl or halogen, and R_{24} is hydrogen.

38. A compound of claim 37 which is

N-[(2-chloro-6-methylphenyl)carbonyl]-4-(5-chloro-1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine;

N-[(2-chloro-6-methylphenyl)carbonyl]-4-(1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine; or

N-[(2-chloro-6-methylphenyl)carbonyl]-4-(1,4-dimethyl-2-oxo-3-pyridinyl)-L-phenylalanine.

39. A compound of claim 36 wherein R_{22} and R_{23} are halogen, and R_{24} is hydrogen.

40. A compound of claim 39 which is N-[(2,6-dichlorophenyl)carbonyl]-4-(1,4-dimethyl-2-oxo-3-pyridinyl)-L-phenylalanine.

41. A compound of claim 36 wherein R_{22} and R_{23} are halogen or hydrogen and R_{24} is lower alkoxy.

42. A compound of claim 41 which is
N-[(2-bromo-5-methoxyphenyl)carbonyl]-4-(1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine; or
N-[(2-bromo-5-methoxyphenyl)carbonyl]-4-(5-bromo-1-methyl-2-oxo-3-pyridinyl)-L-phenylalanine.

43. A compound of claim 35 wherein R_1 is Y-3.

44. A compound of claim 43 which is 4-(5-chloro-1-methyl-2-oxo-3-pyridinyl)-N-[[1-(2-methoxyethyl)cyclopentyl]carbonyl]-L-phenylalanine.

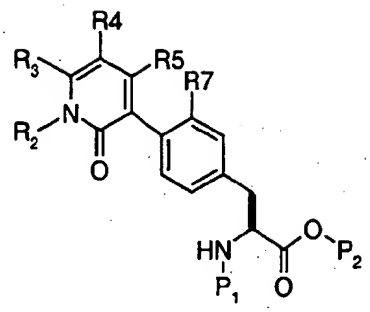
45. A compound of claim 19 wherein R_{22} and R_{23} are halogen or lower alkyl, R_{24} is hydrogen or lower alkoxy, R_{25} is a group of formula $R_{26}—(CH_2)_e—$, wherein R_{26} is lower alkoxy, Q is $-(CH_2)_f-$, e is an integer from 0 to 4 and f is an integer from 0 to 3.

46. A compound of claim 45 wherein R_2 is aryl lower alkyl; R_3 is hydrogen, R_4 is halogen, and R_5, R_6 and R_7 are hydrogen.

47. A compound of claim 46 wherein R_1 is Y-1.

48. A compound of claim 47 which is
4-(1-Benzyl-5-chloro-2-oxo-3-pyridinyl)-N-[(2-chloro-6-methylphenyl)carbonyl]-L-phenylalanine; or
4-(1-Benzyl-5-chloro-2-oxo-3-pyridinyl)- N-[[1-(2-methoxyethyl)-cyclopentyl]carbonyl]-L-phenylalanine.

49. A compound of formula II



II

wherein R^2-R^5 and R^7 are as defined in claim 1 and P_1 and P_2 each are a protecting group.

50. A compound according to any of claims 1-48 for use as a medicament.

51. A pharmaceutical composition comprising a compound according to any one of claims 1-48, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

52. A compound according to any one of claims 1-48 for use in the treatment of disease states mediated by the binding of VCAM-1 or VLA-4 or VLA-4-expressing cells, especially in the treatment of rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease and asthma.

53. The use of a compound to any one of claims 1-48 or a pharmaceutically acceptable salt thereof, in the treatment of disease states mediated by the binding of VCAM-1 or VLA-4 or VLA-4-expressing cells, especially in the treatment of rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease and asthma.

54. A process for the preparation of a pharmaceutical composition which process comprises bringing a compound according to any one of claims 1-48 or a pharmaceutically acceptable salt thereof, and a compatible pharmaceutical carrier into a galenical administration form.

55. The use of a compound according to any one of claims 1-48, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease and asthma.

56. The invention substantially as hereinbefore described, especially with reference to the new compounds, intermediates, pharmaceutical compositions and uses thereof.

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INTERNATIONAL SEARCH REPORT

Inte ›nal Application No
PCT/EP 00/11979

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D213/64 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 43642 A (ARCHIBALD SARAH CATHERINE ;CELLTECH THERAPEUTICS LTD (GB); WARRELL) 2 September 1999 (1999-09-02) claims 1,8 ---	1-56
P,Y	WO 00 43354 A (JOHNSON BRADLEY S ;THORSETT EUGENE D (US); ELAN PHARM INC (US); GR) 27 July 2000 (2000-07-27) claims; example 35 ---	1-56
P,Y	WO 00 37429 A (TANABE SEIYAKU CO ;MATSUKI KENJI (JP); TEEGARDEN BRADLEY R (US); B) 29 June 2000 (2000-06-29) claims -----	1-56

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 March 2001	16/05/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Johnson, C

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ›nal Application No
PCT/EP 00/11979

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9943642 A	02-09-1999	AU 3260399 A	15-09-1999
		EP 1056714 A	06-12-2000
WO 0043354 A	27-07-2000	AU 3348800 A	07-08-2000
WO 0037429 A	29-06-2000	AU 2209500 A	12-07-2000